



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 31

A. R. Katritzky

Advances in  
**Heterocyclic  
Chemistry**

Volume 31

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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1982



Volume 31

**ACADEMIC PRESS**

**A Subsidiary of Harcourt Brace Jovanovich, Publishers**

**New York London**

**Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto**

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ACADEMIC PRESS, INC.  
111 Fifth Avenue, New York, New York 10003

*United Kingdom Edition published by*  
ACADEMIC PRESS, INC. (LONDON) LTD.  
24/28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

ISBN 0-12-020631-5

PRINTED IN THE UNITED STATES OF AMERICA

82 83 84 85    9 8 7 6 5 4 3 2 1

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## Preface

The present volume contains six chapters. The chapter by Dean is the second part of a review on Furans which began in Volume 30. The two parts together update an earlier review of Furans which appeared in Volume 7 (1966) of the series. The contribution by Gurnos Jones on "Aromatic Quinolizines" also updates earlier reviews on this subject which appeared in Volume 5 (1965).

The other four chapters are concerned with topics new to the series. C. Th. Pedersen deals with "1,2-Dithiol-3-thiones and 1,2-Dithiol-3-ones." Perlmutter and Trattner have written the first available comprehensive review of "Diazocines and Triazocines." Kobayashi and Kumadaki have dealt with the interesting topic of "Dewar Heterocycles." Meth-Cohn and Tarnowski have summarized the available work, much of it from their own laboratory, on "Condensations under Vilsmeier Conditions."

A. R. KATRITZKY

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## Aromatic Quinolizines

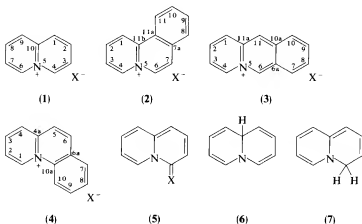
GURNOS JONES

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ST5 5BG, England*

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## I. Introduction

As in the earlier review<sup>1</sup> this account will be restricted to the quinolizinium ion (1), the benzo[*a*]- (2), benzo[*b*]- (3), and benzo[*c*]quinolizinium (4) ions, and to their derivatives. The quinolizones and compounds of similar structure (5) will be included, but the quinolizines (6 and 7) only where they appear as intermediates in synthesis or reaction. A number of trivial and unsystematic names have been used (pyridocolinium ion, dehydroquinolizinium ion for compound 1; acridizinium ion, 4*a*-azoniaanthracene for compound 3; phenanthridizinium ion for compounds 2 or 4), and numbering has also varied. Throughout this chapter the numbering will be as shown in formulas 1 to 4.



## II. Syntheses of Quinolizine Derivatives

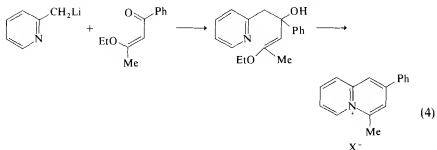
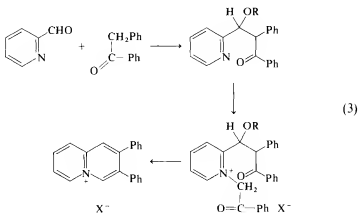
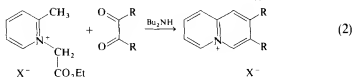
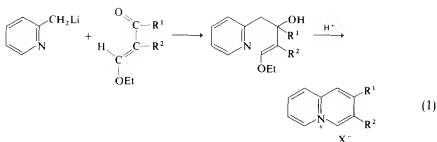
In this section syntheses producing the ring systems will be described; interconversion of functional groups will be found in Section III.

### A. BICYCLIC COMPOUNDS

#### 1. Syntheses Producing Fully Unsaturated Quinolizinium Salts

Syntheses of this type were reported in an earlier review and are summarized in Eqs. (1-4).

<sup>1</sup> B. S. Thyagarajan, *Adv. Heterocycl. Chem.* **5**, 291 (1965).



The routes due to Richards and Stevens<sup>2</sup> (Eq. 1), Westphal and Feix<sup>3,4</sup> (Eq. 3), and Hansen and Amstutz<sup>5</sup> (Eq. 4) have not been further developed.

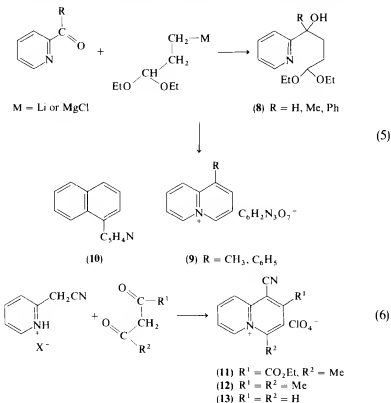
<sup>2</sup> A. Richards and T. S. Stevens, *Chem. Ind. (London)*, 905 (1954).

<sup>3</sup> O. Westphal and G. Feix, *Angew. Chem.* **75**, 206 (1963).

<sup>4</sup> Dr. A. Wander A-G., Swiss Patent 417,601 1967 [*CA* **67**, 90695 (1967)].

<sup>5</sup> H. V. Hansen and E. D. Amstutz, *J. Org. Chem.* **28**, 393 (1963).

A modification in which 2-pyridyl aldehydes or ketones were treated with the lithium or Grignard reagent from  $\beta$ -halogenopropionaldehyde diethylacetals gave the hydroxyacetal **8**; cyclization and dehydration was achieved in two cases, one in low yield, giving 1-phenylquinolizinium picrate (**9**) (Eq. 5).<sup>6</sup> The competing cyclization gave 1-(2-pyridyl)naphthalene (**10**). Some 1-cyanoquinolizinium salts (**11–13**) have been obtained from 2-cyanomethylpyridinium salts and  $\beta$ -dicarbonyl compounds (Eq. 6); malon dialdehyde diethylacetal gave 1-cyanoquinolizinium perchlorate (**13**) in low yield.<sup>7</sup>



An examination of the scope and limitations of the synthesis due to Westphal *et al.*<sup>8</sup> (Eq. 2) was made by Hough and Jones<sup>9</sup> in their attempts to prepare aminoquinolizinium salts. A possible steric inhibition was noted

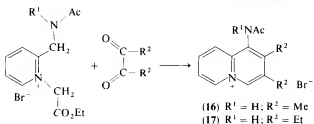
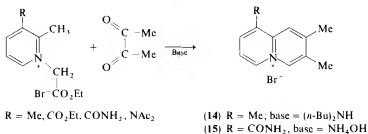
<sup>6</sup> E. E. Glover and G. Jones, *J. Chem. Soc.*, 1686 (1959).

<sup>7</sup> V. A. Chuiguk and Yu. M. Volovenko, *Khim. Geterosikl. Soedin.*, 530 (1975) [*CA* **83**, 116911 (1975)]; U.S.S.R. Patent 486,015 [*CA* **84**, 43867 (1976)].

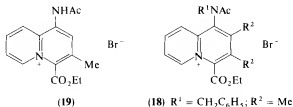
<sup>8</sup> O. Westphal, K. Jann, and W. Heffe, *Arch. Pharm. (Weinheim, Ger.)* **294**, 37 (1961).

<sup>9</sup> T. L. Hough and G. Jones, *J. Chem. Soc. C*, 1082 (1968).

when 3-substituted-2-picolines were used; 1,7,8-trimethylquinolizinium bromide (**14**) was obtained, but other 3-substituted picolinium salts ( $R = \text{CO}_2\text{Et}$ ,  $\text{CONH}_2$ ,  $\text{NAC}_2$ ) gave no quinolizinium salts. By varying the base (aqueous ammonia in place of the di-*n*-butylamine) amide **15** was obtained. A good yield of 2-acetamido-7,8-dimethylquinolizinium bromide was obtained; more surprisingly, adequate yields of the 1-acetamidoquinolizinium salts **16** and **17** were obtained, although steric inhibition to condensation in the acetamidomethylpyridinium salt seems considerable. The complete removal of the carbethoxy group under mild conditions has been puzzling [see also Eq. (3)]. Hough and Jones isolated the 4-ethoxycarbonylquinolizinium salts **18** and **19**. The preparation of **19** is particularly interesting not only because it is the only reported example in which an  $\alpha$ -ketoaldehyde was used, but also because the cyclization demonstrated complete regiospecificity. Intramolecular aldol condensations have been used to provide routes to 3-hydroxyquinolizinium bromide (**20**) (Eq. 7)<sup>10,11</sup>



or



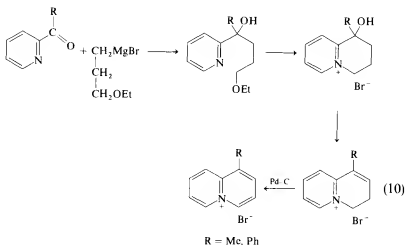
<sup>10</sup> E. Schraufstätter, *Angew. Chem.* **74**, 871 (1961).

<sup>11</sup> P. A. Duke, A. Fozard, and G. Jones, *J. Org. Chem.* **30**, 526 (1965).

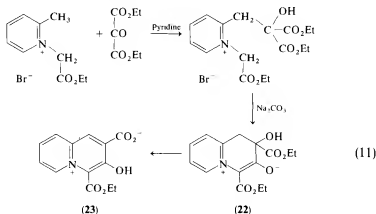




salts described by Glover and Jones<sup>6</sup> (Eq. 10) suffer from the disadvantage of a final heterogeneous dehydrogenation stage, limiting the scale of the syntheses.



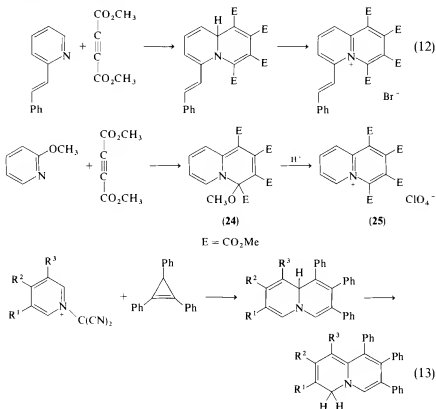
Carelli *et al.*<sup>15</sup> have described a variant of the Westphal, Jann, and Heffe procedure<sup>8</sup> using ketomalonate (Eq. 11), in which the intermediate alcohol **22** is isolated. Further treatment with stronger base causes hydrolysis and dehydration to give the quinolizinium betaine **23**.



A large number of cycloaddition reactions between pyridine or its derivatives and acetylenic esters have been reported, and in many cases these

<sup>15</sup> V. Carelli, F. Liberatore, and G. Casini, *Ann. Chim. (Rome)* **57**, 269 (1967) [*CA* **67**, 54023 (1967)].

give stable *4H*- or *9aH*-quinolizines. Such additions have recently been reviewed.<sup>16</sup> Since, in principle, any of these *4H*- or *9aH*-quinolizines can be oxidized to the quinolizinium salt, this sequence, exemplified by Eq. (12), can be regarded as a general synthesis of highly substituted quinolizinium salts. However, many products are usually obtained in the cycloaddition including indolizines.<sup>16</sup> Acheson and Robinson<sup>17</sup> reported the formation of the 4-methoxy-*4H*-quinolizine **24**, converted by perchloric acid to the tetraethoxycarbonylquinolizinium salt **25**. Matsumoto and Uchida<sup>18</sup> have obtained *9aH*- and *4H*-quinolizines from pyridinium ylids and triphenylcyclopropene (Eq. 13).

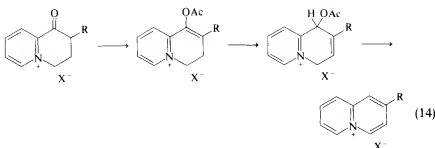


The other major route from hydroquinolizinium salts is the aromatization of 1-keto-1,2,3,4-tetrahydroquinolizinium salts, discovered by Glover and

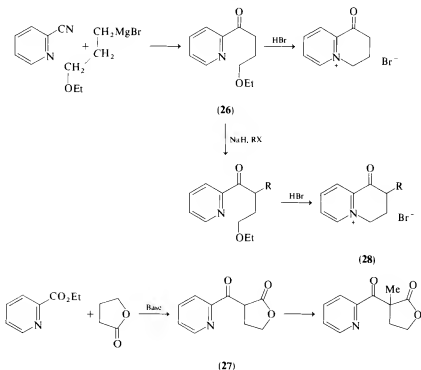
<sup>16</sup> R. M. Acheson and N. F. Elmore, *Adv. Heterocycl. Chem.*, **23**, 263 (1978).

<sup>17</sup> R. M. Acheson and D. A. Robinson, *J. Chem. Soc. C*, 1629 (1968).

<sup>18</sup> K. Matsumoto and T. Uchida, *Synthesis*, 207 (1978).



Jones<sup>19,20</sup> (Eq. 14). Miyadera and Iwai reported an alternative route to the cyclic ketones **28**, which allows of the introduction of a substituent by alkylation of the keto lactone **27**<sup>21</sup>; Hough and Jones<sup>22</sup> subsequently showed that ketone **26** could be alkylated by reactive halides (for example, allyl bromide, giving eventually 2-*n*-propylquinolizinium bromide).



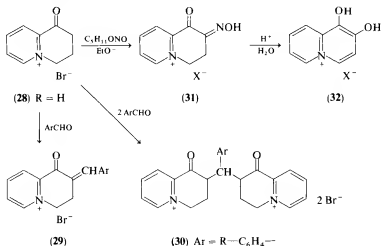
<sup>19</sup> E. E. Glover and G. Jones, *Chem. Ind. (London)*, 1456 (1956).

<sup>20</sup> E. E. Glover and G. Jones, *J. Chem. Soc.*, 3021 (1958).

<sup>21</sup> T. Miyadera and I. Iwai, *Chem. Pharm. Bull.* **12**, 1338 (1964).

<sup>22</sup> T. L. Hough and G. Jones, *J. Chem. Soc. C*, 1112 (1967).

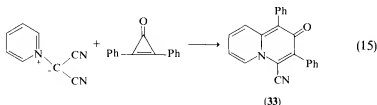
Attempts to prepare 2-benzylidenequinolizinium salts **29** by reaction of ketone **28** ( $R = H$ ) with benzaldehydes failed, bis(2-quinoliziny)aryl-methanes (**30**) being the only isolated products.<sup>22</sup> Treatment of ketone **28** ( $R = H$ ) with amyl nitrite gave an isonitroso derivative (**31**), hydrolyzed to 1,2-dihydroxyquinolizinium bromide (**32**).<sup>9</sup>



### 3. Syntheses Giving Quinolizones and Quinolizine Imines

Syntheses of 2-quinolizones are given first, then 4-quinolizones and 4-quinolizine imines, and finally hydroxyquinolizones.

Pyridinium dicyanomethylide reacts with diphenylcyclopropanone to give the 2-quinolizone **33** (Eq. 15).<sup>23</sup> Other syntheses of 2-quinolizones start from 2-cyanomethyl- or 2-alkoxycarbonylmethylpyridines, which react with diketene (Eq. 16),<sup>24,25</sup> or acetylene dicarboxylate (Eq. 17).<sup>17,26</sup> The reaction



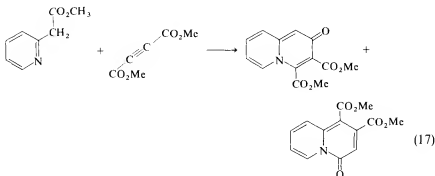
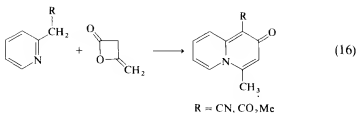
<sup>23</sup> K. Matsumoto, Y. Kono, and T. Uchida, *J. C. S. Chem. Commun.*, 1045 (1976).

<sup>24</sup> T. Kato and T. Atsumi, *Yakugaku Zasshi* **87**, 961 (1967) [*CA* **68**, 49422 (1968)].

<sup>25</sup> T. Kappe, I. Herbst, and E. Ziegler, *Monatsh. Chem.* **100**, 136 (1969).

<sup>26</sup> E. Winterfeldt, *Chem. Ber.* **98**, 3537 (1965).

<sup>27</sup> R. M. Acheson and J. M. Woollard, *J. C. S. Perkin I*, 740 (1975).



with acetylenedicarboxylate is solvent dependent, giving more 2-quinolizone in *tert*-butanol, but a large excess of 4-quinolizone in benzene.

Many syntheses of 4-quinolizones are available, though most start from activated  $\alpha$ -picolines. The reaction with acetylenedicarboxylates (Eq. 17) can be adjusted to maximize 4-quinolizone formation, though additional products of type **34** are often obtained; these are also obtained (Eq. 18) in reactions using methyl propiolate,<sup>17</sup> or but-1-yn-3-one.<sup>28</sup> A 3-(2-pyridyl)-4-quinolizone (**35**) can be obtained from a 2-pyridylacetate and ethyl orthoformate in boiling acetic anhydride.<sup>29</sup> The most versatile synthesis uses the ethoxymethylene derivatives of active methylene compounds, shown in a general form in Eq. (19). Activation of the  $\alpha$ -picoline can be supplied by ester,<sup>30,31</sup> cyano,<sup>32</sup> or ketone<sup>31,33,34</sup> groups; substituents on the ethoxymethylene component can be ester,<sup>30,32</sup> nitro,<sup>33</sup> cyano,<sup>32</sup> ketone,<sup>32,34</sup> or 2-pyridyl.<sup>32</sup>

<sup>28</sup> R. M. Acheson and J. M. Woollard, *J. C. S. Perkin I*, 446 (1975).

<sup>29</sup> G. R. Clemons, W. M. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936); S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, **37**, 1823 (1972).

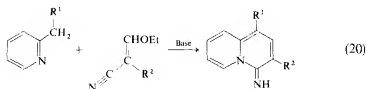
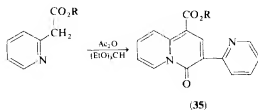
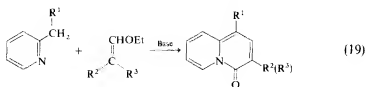
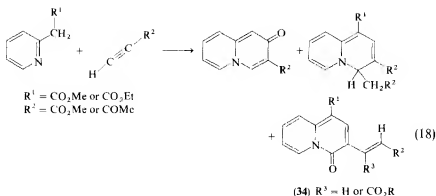
<sup>30</sup> S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, **35**, 242 (1970).

<sup>31</sup> B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **21**, 3305 (1965).

<sup>32</sup> G. Buchmann and W. Duchna, *Pharmazie* **23**, 301 (1968).

<sup>33</sup> B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **21**, 3851 (1965).

<sup>34</sup> B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **23**, 945 (1967).

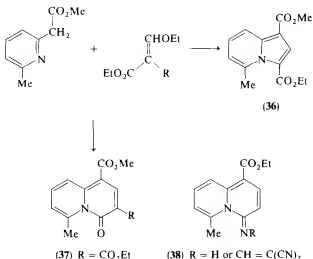


In all cases one of the groups  $R^2$  or  $R^3$  in Eq. (19) has been an ester, and in most cases the ester group cyclizes on to the pyridine nitrogen atom. However, cyclization of a nitrile can give a quinolizidine imine (Eq. 20). In an example where ethyl ethoxymethylene cyanoacetate was used<sup>32</sup> the formation of imine was favored at  $-10^\circ$  but not at higher temperatures where 4-quinolizone becomes the major product. Examples of the reaction (Eq. 20) have been reported where  $R^1$  was a nitrile,<sup>32,35</sup> ester,<sup>32,35,36</sup> or ketone

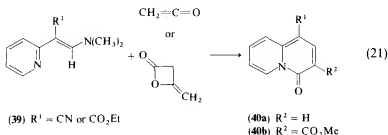
<sup>35</sup> K. Kurata, H. Awaya, C. Maseda, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi* **95**, 1431 (1975) [*CA* **84**, 105434 (1976)].

<sup>36</sup> H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **22**, 1424 (1974).

group,<sup>32</sup> and R<sup>2</sup> a phenyl,<sup>32</sup> 2-pyridyl,<sup>32</sup> cyano,<sup>32,35,36</sup> ketone,<sup>32</sup> or ester.<sup>3</sup> Side products have been reported, particularly when a 2,6-disubstituted pyridine was used. In one case<sup>31</sup> variation in the ethoxymethylene component led to an indolizine (36) or to a quinolizone (37); in another case<sup>36</sup> a substituted imine (38) was obtained. The imines can also form cyclazines<sup>35,36</sup> (see Section IV,E).



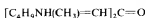
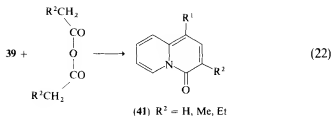
The dimethylaminomethylene derivatives (39) of activated  $\alpha$ -picolines react with ketene or diketene<sup>37</sup> or with a variety of carboxylic acid derivatives<sup>38</sup> to give 4-quinolizones (Eqs. 21–23). Ketene gave the 1-substituted-4-quinolizone (40a), whereas diketene gave the corresponding 3-acetyl derivative (40b).<sup>37</sup> Acid anhydrides gave 4-quinolizones of type 41, while esters of acids with an active methylene group gave 3-substituted-4-quinolizones (42).<sup>38</sup>



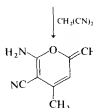
<sup>37</sup> T. Kato and T. Chiba, *Yakugaku Zasshi* **89**, 1464 (1969) [*CA* **72**, 12532 (1970)]

<sup>38</sup> T. Kato, T. Chiba, and S. Tanaka, *Chem. Pharm. Bull.* **22**, 744 (1974).

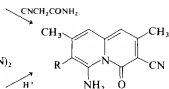




(43)



(44)

(45)  $\text{R} = \text{CN}$ (46)  $\text{R} = \text{CONH}_2$ 

A remarkable synthesis of the heavily substituted 4-quinolizones **45** and **46**, due to Van Allan and Reynolds,<sup>39</sup> starts from the acyclic precursor **43**, or from the  $\alpha$ -pyrone derivative **44**.

From the bismethylthio derivatives **47** or **49** and an activated  $\alpha$ -picoline 2-methylthioquinolizones (**48**)<sup>40</sup> or 2-methylthioquinolizine imine (**50**)<sup>41</sup> have been obtained. An alternative route to 2-methylthio-4-quinolizones started from a pyridylketene dithioacetal and an active methylene compound (Eq. 24).<sup>42</sup> Potts and Sorm<sup>43</sup> have prepared 4-quinolizones from a mesoionic

<sup>39</sup> J. A. Van Allan and G. A. Reynolds, *J. Heterocycl. Chem.* **8**, 923 (1971).

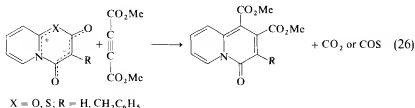
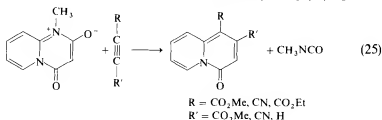
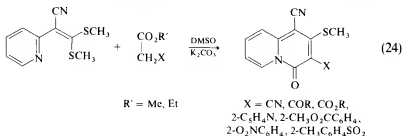
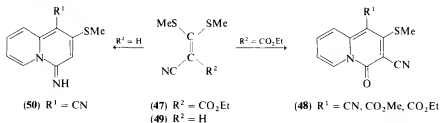
<sup>40</sup> G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *Yakugaku Zasshi* **89**, 203 (1969) [*CA* **70**, 106328 (1969)].

<sup>41</sup> G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, C. Mareca, and H. Awaya, *Yakugaku Zasshi* **94**, 50 (1974) [*CA* **80**, 108339 (1974)].

<sup>42</sup> G. Kobayashi, Y. Matsuda, and R. Natsuki, *Chem. Pharm. Bull.* **21**, 921 (1973).

<sup>43</sup> K. T. Potts and M. Sorm, *J. Org. Chem.* **36**, 8 (1971).

species and acetylenes (Eq. 25). Similar syntheses, using different mesoionic compounds, have been reported by Kappe *et al.*<sup>44,45</sup> (Eq. 26).



A number of 2-hydroxy-4-quinolizones have been prepared by reaction between a substituted  $\alpha$ -picoline and malonyl chloride,<sup>46</sup> or di-(2,4,6-trichlorophenyl) malonate,<sup>46,47</sup> or carbon suboxide,<sup>46,48</sup> as shown in Eq. (27).

<sup>44</sup> T. Kappe, W. Golser, M. Hariri, and W. Stadlbauer, *Chem. Ber.* **112**, 1585 (1979).

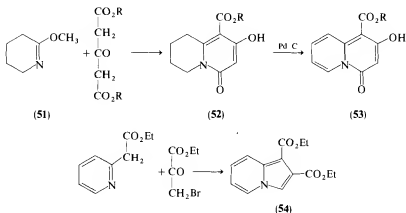
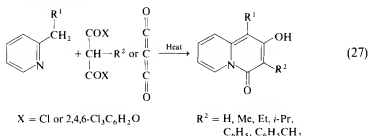
<sup>45</sup> T. Kappe and W. Golser, *Chem. Ber.* **109**, 3668 (1976).

<sup>46</sup> T. Kappe, *Monatsh. Chem.* **98**, 874 (1967).

<sup>47</sup> F. S. G. Soliman and T. Kappe, *Pharmazie* **32**, 278 (1977).

<sup>48</sup> T. Kappe, *Monatsh. Chem.* **98**, 1852 (1967).

The substituent on the methyl group of the  $\alpha$ -picoline can be phenyl or benzyl, but only the malonate ester at 250 C gave successful condensations. In a high temperature reaction between methyl 2-pyridylacetate and the di(trichlorophenyl) malonate, 2-hydroxy-4-quinolizone was formed with loss of the methoxycarbonyl group.<sup>46</sup> The tetrahydropyridine (51) reacted with acetone dicarboxylate to give a tetrahydro-2-hydroxy-4-quinolizone (52), but dehydrogenation to the quinolizone 53 gave only a 5% yield.<sup>49</sup> The 4H-quinolizine-2,3-dione structure proposed<sup>50</sup> for the product of reaction between ethyl 2-pyridylacetate and ethyl bromopyruvate has been corrected to the indolizine diester (54).<sup>51</sup>



## B. TRICYCLIC COMPOUNDS

An excellent review by Bradsher<sup>52</sup> has dealt with benzoquinolizinium salts; hence, work prior to 1968 is only summarized in the present account.

<sup>49</sup> T. Kappe, M. Hariri, and F. S. G. Soliman, *Arch. Pharm. (Weinheim, Ger.)* **309**, 684 (1976).

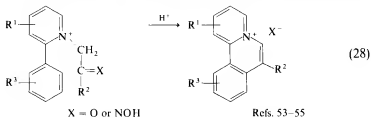
<sup>50</sup> K. Winterfeld and W. Erning, *Arch. Pharm. (Weinheim, Ger.)* **298**, 220 (1965).

<sup>51</sup> T. Kappe, *Monatsh. Chem.* **98**, 1858 (1967).

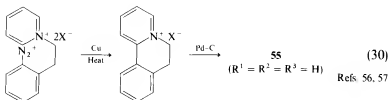
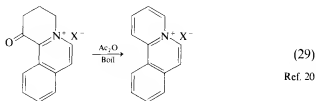
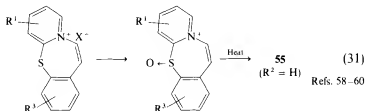
<sup>52</sup> C. K. Bradsher, *Acc. Chem. Res.* **181** (1969).

## 1. Syntheses of Benzo[a]quinolizinium Salts

Up to 1967 benzo[a]quinolizinium salts could be made by the general methods shown in Eqs. (28–32). Two syntheses of benzo[a]quinolizinium



(55)

(R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H)(R<sup>2</sup> = H)

<sup>53</sup> C. K. Bradsher and L. A. Beavers, *J. Am. Chem. Soc.* **77**, 453 (1955).

<sup>54</sup> C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.* **28**, 78 (1963).

<sup>55</sup> R. W. L. Kimber and J. C. Parham, *J. Org. Chem.* **28**, 81 (1963).

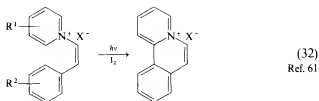
<sup>56</sup> S. Akabashi and T. Kato, *Yakugaku Zasshi* **83**, 1067 (1963) [*CA* **60**, 10647 (1964)].

<sup>57</sup> S. Akabashi, T. Kato, and A. Saiga, *Chem. Pharm. Bull.* **11**, 1446 (1963).

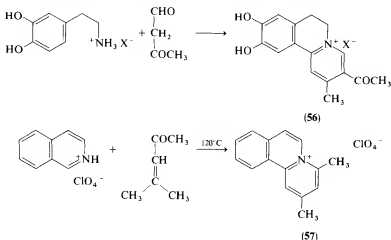
<sup>58</sup> C. K. Bradsher and J. W. McDonald, *J. Org. Chem.* **27**, 4475 (1962).

<sup>59</sup> C. K. Bradsher and J. W. McDonald, *J. Org. Chem.* **27**, 4478 (1962).

<sup>60</sup> C. K. Bradsher and D. F. Lohr, Jr., *J. Org. Chem.* **31**, 978 (1966).



salts are unrecorded in the review.<sup>52</sup> Teuber and Laudien<sup>62</sup> reported that Dopamin reacts with acetoacetaldehyde to give directly a substituted 6,7-dihydrobenzo[*a*]quinolinizinium salt (**56**), aromatized by treatment with chloranil. The intermediate was thought to be a 1-acetonilytetrahydroisoquinoline, which reacts with a second molecule of acetoacetaldehyde on the nitrogen atom with subsequent cyclization to give ring A. Chapman<sup>63</sup> reported the annulation of isoquinolinium perchlorate by 4-methylpent-3-en-2-one to give 2,4-dimethylbenzo[*a*]quinolinizinium perchlorate (**57**).



## 2. Syntheses of Benzo[*b*]quinolinizinium Salts

There are only two general syntheses of benzo[*b*]quinolinizinium salts, shown in Eqs. (33 and 34). The former, due to Bradsher and co-workers<sup>64-69</sup>

<sup>61</sup> R. E. Doolittle and C. K. Bradsher, *J. Org. Chem.* **31**, 2616 (1966).

<sup>62</sup> H.-J. Teuber and D. Laudien, *Chem. Ber.* **100**, 35 (1967).

<sup>63</sup> D. D. Chapman, *J. C. S. Chem. Commun.*, 489 (1975).

<sup>64</sup> C. K. Bradsher and L. Beavers, *J. Am. Chem. Soc.* **77**, 4812 (1955).

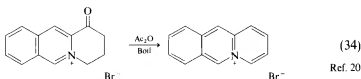
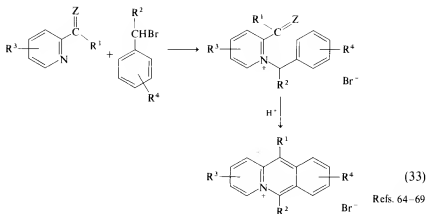
<sup>65</sup> C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.* **25**, 757 (1960).

<sup>66</sup> C. K. Bradsher and J. C. Parham, *J. Org. Chem.* **28**, 83 (1963).

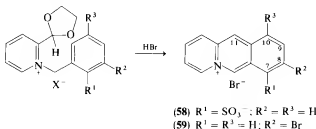
<sup>67</sup> C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.* **1**, 30 (1964).

<sup>68</sup> C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.* **81**, 2550 (1959).

<sup>69</sup> C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.* **1**, 121 (1964).



has been used with modifications to produce almost all the known salts. A number of examples of the Bradsher synthesis illustrate its scope. Deactivated benzene rings can take part in the cyclization as shown by the production of zwitterion **58**,<sup>70</sup> and by the synthesis of 8-bromo- (**59**) and 7,10-dichlorobenzo[*b*]quinolizinium salts.<sup>71</sup> The cyclization of the *m*-bromobenzylpyridinium salt gave only the 8-bromo derivative indicating regioselectivity. Fields *et al.*<sup>72</sup> reported the synthesis of a number of hydroxybenzo[*b*]quinolizinium salts, starting with the acetates. Fields and Miller<sup>73</sup> also reported failure in attempts to cyclize the *t*-butyl derivative **60**, although the very similar compound **61** was successfully converted to the benzoquinolizinium salt **62**. In another case where steric hindrance might have

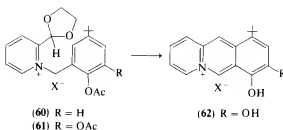


<sup>70</sup> C. K. Bradsher, J. C. Parham, and J. D. Turner, *J. Heterocycl. Chem.*, **2**, 228 (1965).

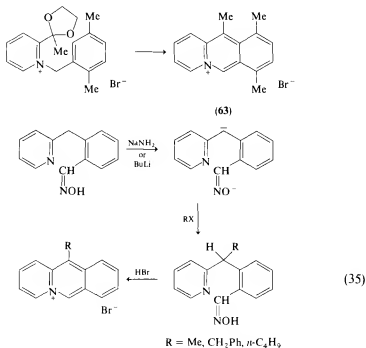
<sup>71</sup> J. D. Turner and C. K. Bradsher, *J. Org. Chem.*, **32**, 1169 (1967).

<sup>72</sup> D. L. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **30**, 252 (1965).

<sup>73</sup> D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.*, **7**, 91 (1970).



been expected, Hart *et al.*<sup>74</sup> obtained a quantitative yield of 7,10,11-trimethylbenzo[*b*]quinolinizinium bromide (**63**). In a variation the dianion of 2-(2-pyridylmethyl)benzaloxime was alkylated on the methylene carbon giving 11-substituted quinolinizinium salts (Eq. 35).<sup>75</sup>



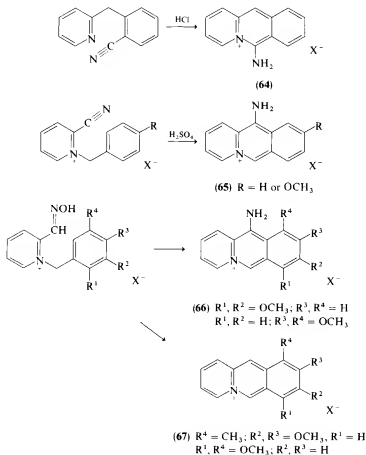
By cyclization of 2-(*o*-cyanobenzyl) pyridine in acid Bradsher and Sherer<sup>76</sup> obtained 6-aminobenzo[*b*]quinolinizinium salts **64**. A variation gave 11-

<sup>74</sup> H. Hart, J. B. C. Jiang, and R. K. Gupta, *Tetrahedron Lett.*, 4639 (1975).

<sup>75</sup> G. Crowther, M. Y. Johnson, and C. K. Bradsher, *J. Heterocycl. Chem.* **8**, 157 (1971).

<sup>76</sup> C. K. Bradsher and J. P. Sherer, *J. Org. Chem.* **32**, 733 (1967).

aminobenzo[*b*]quinolizinium salts **65**.<sup>77</sup> Careful study of the cyclization using a 2-pyridaldoxime as starting material reveals that the product may be the amine, as in **66**, or the normal product, as in **67**.<sup>78,79</sup> The crucial point seems to be the presence of a methoxyl group para to the point of cyclization with another, neighboring methoxyl group. However, steric hindrance may slow down cyclization so that oxime hydrolysis competes when the "normal" product is obtained.



<sup>77</sup> C. K. Bradsher and L. S. Davies, *J. Org. Chem.* **38**, 4167 (1973).

<sup>78</sup> J. W. H. Watthey, K. J. Doebel, F. H. Vernay, and A. L. Lopano, *J. Org. Chem.* **38**, 4170 (1973).

<sup>79</sup> K. J. Doebel and J. W. H. Watthey, South African Patent 67, 07635 [*CA* **70**, 96652 (1969)].

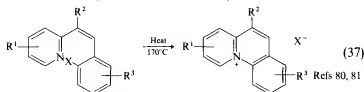
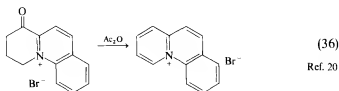
<sup>80</sup> A. Fozard and C. K. Bradsher, *Chem. Commun.*, 288 (1965).

<sup>81</sup> A. Fozard and C. K. Bradsher, *J. Org. Chem.* **31**, 2346 (1966).

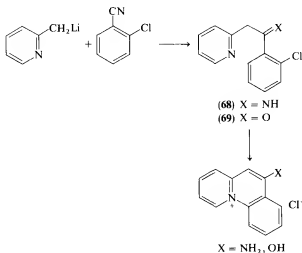


### 3. Syntheses of Benzo[c]quinolizinium Salts

Only two syntheses of benzo[c]quinolizinium salts were available at the time of Bradsher's<sup>52</sup> review. These are shown in Eqs. (36 and 37). A variation of the Fozard and Bradsher synthesis was provided by cyclization of the imine **68**, or the ketone **69**, to give, respectively, 6-amino- or 6-hydroxybenzo[c]quinolizinium salts in good overall yield.<sup>82</sup> Dimroth and Odenwaelder<sup>83</sup> heated pyrylium salts with *o*-aminobenzaldehyde to give alkyl and arylbenzo[c]quinolizinium salts (Eq. 38), probably via the pyridinium salts. This

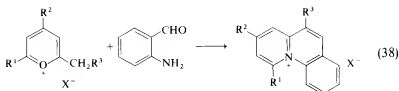


From irradiation of *trans*-stilbazole



<sup>82</sup> J. M. Vierfond, Y. Mettey, R. Joubin, and M. Miocque, *J. Heterocycl. Chem.* **16**, 753 (1979).

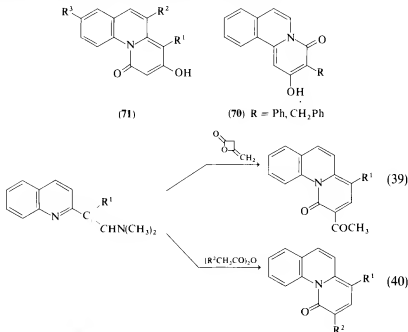
<sup>83</sup> K. Dimroth and H. Odenwaelder, *Tetrahedron Lett.*, 553 (1971).



method allows access to 1-substituted benzo[c]quinolizinium salts ( $\text{R}' = \text{C}_6\text{H}_5$  or  $\text{CH}_3$ ), which are inaccessible by the Fozard and Bradsher synthesis due to steric hindrance.

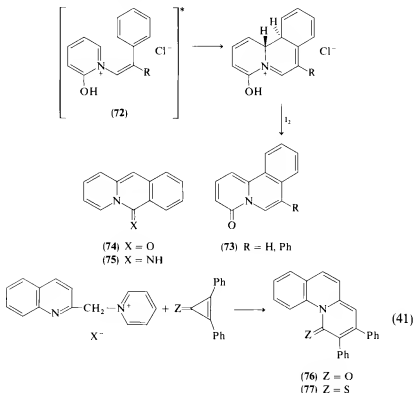
#### 4. Syntheses of Benzoquinolizones and Imines

In principle, most of the syntheses of quinolizones could be applied to the synthesis of benzoquinolizones by starting with the quinoline or isoquinoline equivalent of the pyridine component. Thus Kappe<sup>84</sup> has obtained the hydroxybenzo[a]quinolizin-4-ones **70**, and the hydroxybenzo[c]quinolizin-1-ones **71** from methylquinolines, quinolyl- or isoquinolylacetates, and malonic esters or carbon suboxide. Kato and co-workers<sup>37,38</sup> have used the Vilsmeier derivatives of 2-quinolylacetate with diketene (Eq. 39)<sup>37</sup> or with anhydrides (Eq. 40)<sup>38</sup> to give benzo[c]quinolizin-1-ones.



<sup>84</sup> T. Kappe, *Monatsh. Chem.* **98**, 2148 (1967).

A photochemical route to benzo[*a*]quinolizin-4-ones (73) from 1-styryl-2-pyridones has been reported by Mariano *et al.*<sup>85</sup> Acid was found to be essential and the cyclization was thought to proceed through the excited enol 72, with eventual oxidation by air or by added iodine. Benzo[*b*]quinolizin-6-one (74)<sup>76</sup> and the corresponding imine (75)<sup>86</sup> have been prepared by cyclization of 2-(2-carboxybenzyl)pyridine and 2-cyanobenzylpyridine, respectively. Eicher and Hansen<sup>87</sup> have reported two routes to a benzo[*c*]quinolizin-1-one (76) (Eqs. 41 and 42) and one to the 1-thione 77 (Eq. 41). Treatment of quinoline *N*-oxide with 1,1-dicyanoalkenes also led to benzo[*c*]quinolizin-1-ones (Eq. 43),<sup>88</sup> while the same *N*-oxide with the sulfur ylid 78 gave a benzo[*c*]quinolizin-3-one.<sup>89</sup>



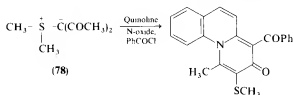
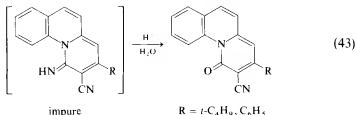
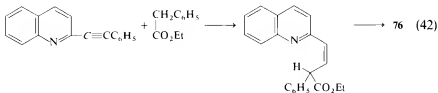
<sup>85</sup> P. S. Mariano, E. Krochmal, Jr., and A. Leone, *J. Org. Chem.* **42**, 1122 (1977).

<sup>86</sup> C. K. Bradsher and I. J. Westerman, *J. Org. Chem.* **43**, 3536 (1978).

<sup>87</sup> T. Eicher and A. Hansen, *Tetrahedron Lett.*, 1169 (1967).

<sup>88</sup> J. E. Douglass and D. A. Hunt, *J. Org. Chem.* **42**, 3974 (1977).

<sup>89</sup> M. Watanabe, M. Kodera, T. Kinoshita, and S. Furukawa, *Chem. Pharm. Bull.* **23**, 2598 (1975).



### III. Properties of the Aromatic Quinolizines

#### A. PHYSICAL PROPERTIES AND THEORETICAL CHEMISTRY

##### 1. Theoretical Chemistry, Ultraviolet and Visible Spectra

Since the last review<sup>1</sup> a few calculations have been reported on quinolizinium salts. Flurry<sup>90</sup> used the Pariser-Parr-Pople SCMO method to calculate ionization potential and  $\pi \rightarrow \pi^*$  transitions. Galasso<sup>91</sup> used the same technique to calculate electron densities, bond orders, and electronic transitions, arriving at the unlikely conclusion that nucleophilic attack should occur at position 3; he subsequently reported a CNDO-2 calculation according to the method of Pople, Santry, and Segal, using all valence electrons.<sup>92</sup> By the latter method the  $\pi$ -electron densities were more in accord with expectation. Finally, Yoshida and Kobayashi<sup>93</sup> have used their variable integral method to calculate electronic transitions in the quinolizinium ion and compare these with the observed values.

<sup>90</sup> R. L. Flurry, Jr., E. W. Stout, and J. J. Bell, *Theor. Chim. Acta* **8**, 203 (1967).

<sup>91</sup> V. Galasso, *Theor. Chim. Acta* **11**, 417 (1968).

<sup>92</sup> V. Galasso, *Gazz. Chim. Ital.* **99**, 1078 (1969).

<sup>93</sup> Z. Yoshida and T. Kobayashi, *Theor. Chim. Acta* **20**, 216 (1971).

Their calculated value for the  $\pi$ -ionization potential was 14.111 eV; no experimental value is available. Galasso<sup>94</sup> has also used Pariser–Parr–Pople calculations on the three benzoquinolizinium ions to produce charge densities and transition energies. Molecular orbital calculations of LUMO and HOMO levels in the benzo[*b*]quinolizinium ion have been used in a discussion of the mechanism of cationic polar cycloaddition (Section IV.E).<sup>95</sup> The binding energy of the positive nitrogen in the benzoquinolizinium salts has been measured relative to that of nitrate, and has been found to be 7.8–8.1 eV.<sup>96</sup>

The electronic absorption spectra of the quinolizinium ion<sup>97</sup> and of a number of benzo[*c*]quinolizinium salts<sup>83</sup> have been reported. Bendig, Kreysig, and co-workers in a series of papers thoroughly explored the fluorescence quenching of the benzo[*b*]quinolizinium ion by alkyl and aryl halides.<sup>98–101</sup> Correlations were made between the rate constants of quenching and the ionization potentials of donors.<sup>100,101</sup> The same authors studied the charge transfer complexes between benzo[*b*]quinolizinium salts and hydrocarbons,<sup>102,103</sup> and the quenching of fluorescence by naphthalene.<sup>104</sup> The quantum yield for dimerization of the benzo[*b*]quinolizinium ion was examined<sup>105</sup>; heavy atom compounds, electron donors, and anions of high polarizability were found to cause a decrease in quantum yields. A charge transfer complex was felt to be important in the early stages of cationic polar cycloaddition and such a complex was observed between benzo[*b*]quinolizinium salts and *N*-vinylcarbazole.<sup>105</sup>

The  $pK_a$  values have been determined spectroscopically for the 2-hydroxyquinolizinium ion<sup>106</sup> and all four hydroxyquinolizinium species.<sup>107</sup> In the detailed study<sup>107</sup> which included related aromatic systems some attempts were made at a correlation of  $pK_a$  and effective  $\pi$ -electron density. The  $pK_a$

<sup>94</sup> V. Galasso, *Gazz. Chim. Ital.* **100**, 421 (1970).

<sup>95</sup> N. A. Porter, I. J. Westerman, T. G. Wallis, and C. K. Bradsher, *J. Am. Chem. Soc.* **96**, 5104 (1974).

<sup>96</sup> J. J. Jack and D. M. Hercules, *Anal. Chem.* **43**, 729 (1971).

<sup>97</sup> S. Pavelka and J. Kovar, *Collect. Czech. Chem. Commun.* **41**, 3654 (1976).

<sup>98</sup> J. Bendig, S. Helm, and D. Kreysig, *Z. Chem.* **17**, 450 (1977).

<sup>99</sup> J. Bendig and D. Kreysig, *Z. Phys. Chem. (Leipzig)* **259**, 173 (1978).

<sup>100</sup> J. Bendig, S. Helm, and D. Kreysig, *J. Prakt. Chem.* **319**, 807 (1977).

<sup>101</sup> J. Bendig, S. Helm, and D. Kreysig, *Chem. Phys. Lett.* **54**, 466 (1978).

<sup>102</sup> J. Bendig and D. Kreysig, *Z. Chem.* **18**, 33 (1978).

<sup>103</sup> J. Bendig and D. Kreysig, *Z. Phys. Chem. (Leipzig)* **259**, 551 (1978).

<sup>104</sup> J. Bendig, B. Geppert, and D. Kreysig, *J. Prakt. Chem.* **320**, 739 (1978).

<sup>105</sup> C. K. Bradsher, G. L. B. Carlson, N. A. Porter, I. J. Westerman, and T. G. Wallis, *J. Org. Chem.* **43**, 822 (1978).

<sup>106</sup> A. Fozard and G. Jones, *J. Chem. Soc.*, 2760 (1964).

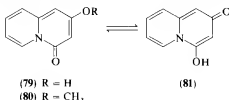
<sup>107</sup> M. Hida and S. Kawakami, *Nippon Kagaku Zasshi*, 1249 (1978) [*CA* **90**, 5734 (1979)].

values obtained are listed in the following:

Hydroxyquinolizinium ion	1	2*	3	4
$pK_a$	$5.03 \pm 0.69$	$4.14 \pm 0.66$	$5.06 \pm 0.47$	$< 2$

\* 4 (Ref. 106).

Tautomerism of 2-hydroxy-4-quinolizones (**79**  $\rightleftharpoons$  **81**) was examined by comparison of the ultraviolet absorption of 2-methoxy-4-quinolizone (**80**) with that of the predominant tautomer (**79**) of the parent.<sup>46</sup>



## 2. Infrared Spectra

No systematic studies of the infrared spectra of the unsubstituted or alkyl or aryl substituted quinolizinium salts have been published. The only compounds where the infrared spectra have been substantially used in structure determination are the 2- or the 4-quinolizones. Fozard and Jones prepared the unsubstituted 2-quinolizone<sup>106</sup> and assigned an absorption at  $1634 \text{ cm}^{-1}$  as the carbonyl stretching band; Kappe *et al.*<sup>25</sup> corrected this assignment by reference to the spectrum of  $\gamma$ -pyridone, and assigned a band at  $1565 \text{ cm}^{-1}$  to carbonyl stretching, and the band near  $1630 \text{ cm}^{-1}$  to double bond stretching. The carbonyl absorption of 4-quinolizones is found in the region  $1675\text{--}1690 \text{ cm}^{-1}$ , with the strong double bond stretch near  $1640 \text{ cm}^{-1}$ . The carbonyl band in 2-hydroxy-4-quinolizones varies from  $1630 \text{ cm}^{-1}$  to  $1590 \text{ cm}^{-1}$ , because of hydrogen bonding.<sup>46</sup>

## 3. NMR Spectra

While many individual quinolizines have been reported with full  $^1\text{H}$ -NMR data, there has been no systematic study. The only outstanding feature of the unsubstituted quinolizinium salts **1** is a downfield broadened doublet at  $\delta 9.0$  due to the highly deshielded 4 and 6 protons.<sup>108</sup> Similarly, the most

<sup>108</sup> G. Jones, unpublished results.

readily observed signals in the benzo[*a*]-, benzo[*b*]-, and benzo[*c*]quinolizinium salts (**2**–**4**) are due to the deshielded protons next to the nitrogen atom. All the coupling constants have been calculated and experimentally determined for 4-quinolizone (**82** ↔ **83**). An estimate of the interaction between olefin residues and a nitrogen lone pair led to a suggestion of 40% contribution by the dipolar species (**83**).<sup>109</sup>



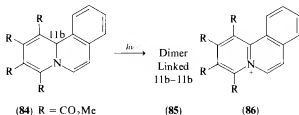
(82)



(83)

#### 4. Mass Spectra

There are no reports of the mass spectra of quinolizinium salts, although the quinolizinium ion, or radical ion, has been suggested to represent one of the fragment ions from 1-(2-pyridyl)butadiene<sup>110</sup> and from 2-methylindolizine.<sup>111</sup> The benzo[*c*]quinolizine (**84**) formed a photodimer (**85**); a major ion in the mass spectrum of the dimer was attributed to the benzo[*c*]quinolizinium ion (**86**).<sup>112</sup>



#### 5. Other Physical Properties

A correlation has been made between the Hammett substituent constants for 9-substituted benzo[*b*]quinolizinium salts and the rate of cycloaddition<sup>113</sup>; this, and the measured Arrhenius parameters for the same

<sup>109</sup> P. Crews, R. R. Kintner, and H. C. Padgett, *J. Org. Chem.*, **38**, 4391 (1973).

<sup>110</sup> A. Maquestiau, Y. Van Haverbeke, and C. De Meyer, *Bull. Soc. Chim. Belg.*, **83**, 147 (1974).

<sup>111</sup> G. Jones and J. Stanyer, *Org. Mass Spectrom.*, **3**, 1489 (1970).

<sup>112</sup> A. O. Plunkett, *J. Chem. Soc. D*, 1044 (1969).

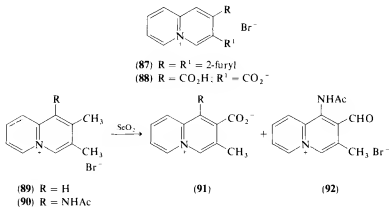
<sup>113</sup> I. J. Westerman and C. K. Bradsher, *J. Org. Chem.*, **36**, 969 (1971).

reaction,<sup>114</sup> are dealt with in more detail in Section IV,E. The temperature dependence of the a.c. and d.c. conductivities and the dielectric constants of benzo[*b*]quinolizinium salts of TCNQ have been recorded and interpreted.<sup>115</sup> The conductivity of solid benzo[*b*]quinolizinium bromides is much higher than that of the benzo[*b*]quinolizinium sulfonate zwitterion; the charge is probably carried by the bromide ions.<sup>116</sup>

#### IV. Chemical Properties

### A. OXIDATION

The chemical properties of the aromatic quinolizines reflect the stability of the ring systems. The bicyclic quinolizinium salts are stable to many oxidizing agents. For example, hot dilute nitric acid is without effect on quinolizinium bromide.<sup>108</sup> Concentrated nitric acid converted 2,3-di(2-furyl)quinolizinium bromide (**87**) to the zwitterion (**88**) without breakdown of the quinolizinium ring.<sup>117</sup> Zwitterions **91** were also obtained by selenium dioxide oxidation of methylquinolizinium salts **89** and **90**; in the latter case the corresponding aldehyde (**92**) was obtained.<sup>9</sup> More surprising was the stability of 4-quinolizones toward hot nitric acid, the products being nitroquinolizones.<sup>34</sup>



<sup>114</sup> C. K. Bradsher, T. G. Wallis, I. J. Westerman, and N. A. Porter, *J. Am. Chem. Soc.*, **99**, 2588 (1977).

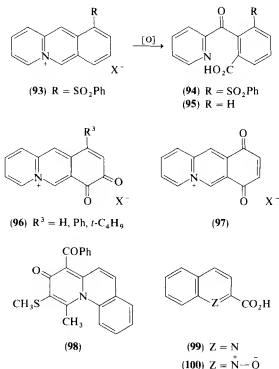
<sup>115</sup> A. A. Gogolin, S. P. Zolotukhin, V. I. Mel'nikov, E. I. Rashba, and I. F. Shchegolev, *Pis'ma Zh. Eksp. Teor. Fiz.*, **22**, 564 (1975) [*CA* **84**, 52734 (1978)].

<sup>116</sup> J. Bashaw and P. M. Gross, *J. Am. Chem. Soc.*, **90**, 3120 (1968).

<sup>(17)</sup> W. K. Gibson and D. Leaver, *J. Chem. Soc. C*, 324 (1966).



By contrast there are a number of cases of oxidative degradation of benzoquinolizines. Bradsher and co-workers used hot dilute nitric acid to oxidize benzo[*b*]quinolizinium salts in order to establish the position of entry of electrophiles. Such an oxidation gave, for example, 2-(2-carboxy-6-phenylsulfonylbenzoyl)pyridine (**94**) from the phenylsulfonylbenzo[*b*]quinolizinium salt (**93**).<sup>118</sup> Benzo[*b*]quinolizinium bromide can be oxidized by permanganate to 2-(2-carboxybenzoyl)pyridine (**95**),<sup>119</sup> and not to phthalic acid as previously reported. Since the oxidations involve the breaking of the 5,6-bond it is tempting to suggest that the well-known susceptibility to attack at the 6-position by nucleophiles may be involved. Oxidation of 7,8- or 7,10-dihydroxybenzo[*b*]quinolizinium salts (cf. **3**) with nitric acid at room temperature gave the corresponding *o*- or *p*-quinones **96** or **97**.<sup>73</sup> Quinoline-2-carboxylic acid (**99**) was obtained by oxidation of benzo[*c*]-



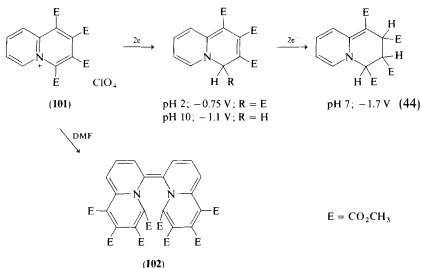
<sup>118</sup> C. K. Bradsher and J. D. Turner, *J. Org. Chem.*, **31**, 565 (1966).

<sup>119</sup> C. K. Bradsher, L. L. Braun, J. D. Turner, and G. L. Walker, *J. Org. Chem.*, **39**, 1157 (1974).

quinolizinium chloride (**4**),<sup>120</sup> whereas 8-quinolizinone (**98**)<sup>89</sup> gave the corresponding *N*-oxide (**100**).

### B. REDUCTION, INCLUDING ADDITION REACTIONS OTHER THAN CYCLOADDITION

Polarographic or electrochemical reductions have been reported for quinolizinium salts and for benzoquinolizinium salts. Controlled-potential electrolysis of the tetramethoxycarbonyl quinolizinium perchlorate (**101**) proceeded as shown in Eq. (44) for an aqueous phase with a mercury cathode.<sup>121</sup> In dimethylformamide at a potential of  $-0.5$  V the red dimer **102** was obtained.



The polarographic reduction of benzo[*a*]- and benzo[*b*]quinolizinium salts has been examined by Frost and Saylor.<sup>122,123</sup> Three derivatives of the benzo[*a*]quinolizinium ion were examined; all showed one wave independent of pH, ascribed to the 2-electron process shown in Eq. (45). The

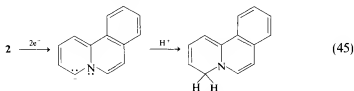
<sup>120</sup> A. Fozard, L. S. Davies, and C. K. Bradsher, *J. Chem. Soc. C*, 3650 (1971).

<sup>121</sup> S. Kato, Y. Tanaka, and J. Nakaya, *Denki Kagaku Kogyo Butsuri Kagaku* **42**, 223 (1974) [*CA* **81**, 135919 (1974)].

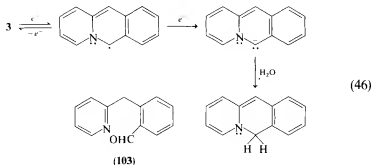
<sup>122</sup> J. G. Frost and J. H. Saylor, *Recl. Trav. Chim. Pays-Bas* **82**, 828 (1963).

<sup>123</sup> J. G. Frost and J. H. Saylor, *Recl. Trav. Chim. Pays-Bas* **83**, 340 (1964).

7,11-dimethyl derivative had a half-wave potential less negative than those of the 7-methyl or 7,10-dimethyl derivatives, an effect ascribed to some loss of planarity because of steric hindrance.

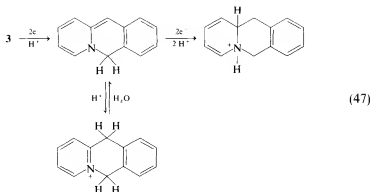


The polarographic reduction of benzo[*b*]quinolizinium salts varied with pH. At pH 1.9 to 7 two waves were observed, the first (half-wave  $-0.807$  V) a one-electron reversible reduction, the second (half-wave  $-1.022$  V) irreversible and diffusion controlled. The proposed pathway is shown in Eq. (46). The reduction in basic medium also had two waves (half-wave potentials about  $-1.5$  and  $-2.2$  V) due to the reduction of aldehyde **103**, a known product of nucleophilic attack at position 6 in benzo[*b*]quinolizinium salts. The changes in reduction potential produced by substituents on the benzo[*b*]quinolizinium ion were examined (19 examples).<sup>123</sup> Various explanations based on inductive and mesomeric effects were offered for observed variations.

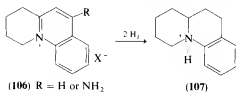
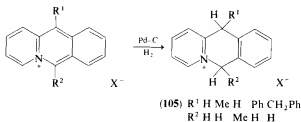
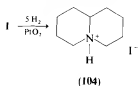


A study of the reduction of benzo[*b*]quinolizinium perchlorate by cyclic voltammetry showed two waves, both irreversible.<sup>124</sup> The first wave was due to addition of two electrons in the rate determining step, the second also due to two electrons, but only one electron being involved in the rate determining step. A tentative proposal for the mechanism of reduction is shown in Eq. (47). The same authors examined the polarographic reduction in anhydrous dimethylformamide; although a one-electron reversible process was indicated, no ESR evidence for free radicals could be obtained.

<sup>124</sup> E. C. Toren, Jr., J. E. Davis, S. K. Nutt, and R. N. Carey, *Fresenius' Z. Anal. Chem.* **264**, 29 (1973).



No systematic study of catalytic hydrogenation of quinolinizinium salts is available. In most cases reduction has been by palladium or platinum with hydrogen at atmospheric pressure to yield the decahydro derivative (the quinolizidine). The first example is provided by Boekelheide and Gall,<sup>125</sup> who produced quinolizidine (104). Benzo[*b*]quinolinizinium salts are catalytically reduced first in the central ring to give 6,11-dihydro derivatives (105).<sup>126</sup> Benzo[*c*]quinolinizinium salts (cf. 4) can be reduced in two stages.<sup>120</sup>

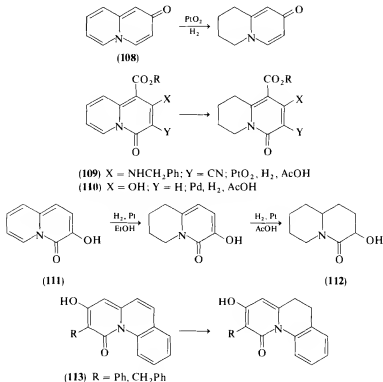


<sup>125</sup> V. Boekelheide and W. G. Gall, *J. Am. Chem. Soc.* **76**, 1832 (1954).

<sup>126</sup> L. L. Braun and C. K. Bradsher, *J. Org. Chem.* **33**, 1296 (1968).

With palladium as catalyst a tetrahydro derivative (**106**) is obtained,<sup>82,120</sup> which can be further reduced with a platinum catalyst to the octahydro derivative (**107**).<sup>120</sup>

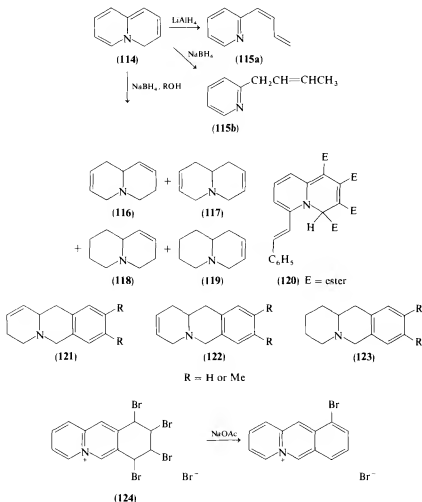
Catalytic reduction of quinolizones was mentioned briefly in the earlier review.<sup>1</sup> For bicyclic quinolizones the reduction invariably proceeds first in the ring remote from the carbonyl group to give a 5,6,7,8-tetrahydro-2- or -4-quinolizone as shown by the reduction of 2-quinolizone (**108**),<sup>106</sup> 4-quinolizone (**109**),<sup>127</sup> 2-hydroxy-4-quinolizone (**110**),<sup>48</sup> and 3-hydroxy-4-quinolizone (**111**).<sup>11</sup> Further reduction gives an octahydroquinolizone such as (**112**).<sup>11</sup> Reduction of the 2-hydroxybenzo[*a*]quinolizin-4-ones (**113**) gave a dihydro derivative.<sup>84</sup>



Reduction of quinolizinium salts by metal hydrides goes through the 4*H*-quinolizine (**114**). With the parent compound, reduction by lithium aluminum hydride was thought to give the 2-pyridylbutadiene (**115a**) while

<sup>127</sup> G. Kobayashi, S. Furakawa, Y. Matsuda, R. Natsuki, and S. Matsunaga, *Yakugaku Zasshi* **90**, 127 (1970) [*CA* **72**, 100467 (1970)].

borohydride in tetrahydrofuran gave the pyridylbutene (**115b**). With borohydride in protic solvents, a mixture of reduction products (**116–119**) was obtained with no ring cleavage.<sup>128</sup> This different behavior was rationalized as solvent dependency, the protic solvents protonating the intermediate 4*H*-quinolizine (enamine) to give iminium salts which were further reduced. Acheson and Feinberg<sup>128a</sup> were able to isolate a stable 4*H*-quinolizine (**120**) by borohydride reduction of a highly substituted quinolizinium salt.<sup>16</sup>



<sup>128</sup> T. Miyadera and Y. Kishida, *Tetrahedron* **25**, 397 (1969).

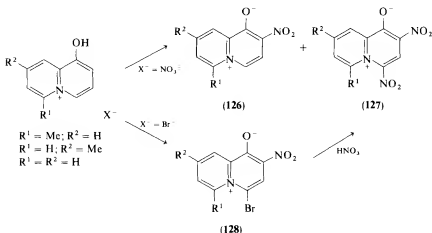
<sup>128a</sup> R. M. Acheson and R. S. Feinberg, *J. Chem. Soc. (C)*, 351 (1968).

Miyadera also studied borohydride reduction of benzo[*b*]quinolizinium salts (cf. **3**) obtaining the hexahydro derivatives **121** and **122**, and the octahydro derivative **123**.<sup>129</sup> It has been shown that bromine adds to benzo[*b*]quinolizinium bromide (**3**) to give a tetrabromo derivative (**124**), from which 10-bromobenzo[*b*]quinolizinium bromide (**125**) was obtained after treatment with sodium acetate.<sup>71</sup>

### C. ELECTROPHILIC SUBSTITUTION

An aromatic system carrying a positive charge is unlikely to undergo attack by electrophiles unless some degree of activation by substituents is available. The bicyclic quinolizinium salts require electron-donating substituents as powerful as the hydroxyl or the amino group before electrophilic substitution occurs. The more distant benzenoid ring of the benzoquinolizinium salts can be directly attacked under vigorous electrophilic conditions; substitution on the rings sharing the positively charged nitrogen atom has not been reported.

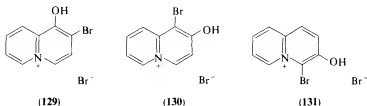
The hydroxyquinolizinium salts (or quinolizones) have all been shown to react with electrophiles. Fozard and Jones<sup>130</sup> have reported that 1-hydroxyquinolizinium salts can be nitrated by hot dilute nitric acid or by a mixture of concentrated nitric acid and acetic anhydride at 0° C. From 1-hydroxyquinolizinium nitrate the products were the 2-nitro- (**126**) and the 2,4-dinitroquinolizinium (**127**) betaines. When the bromide was nitrated a



<sup>129</sup> T. Miyadera and R. Tsuchikawa, *Tetrahedron* **25**, 5189 (1969).

<sup>130</sup> A. Fozard and G. Jones, *J. Chem. Soc.*, 3030 (1964).

third product, the bromonitro derivative (128) was obtained. Since the bromonitro derivative (128) could be converted to the dinitro derivative (127) the bromine atom is probably introduced via free bromine produced by nitric acid oxidation. Evidence for steric hindrance was provided by the failure of a 6-methyl-1-hydroxyquinolizinium salt to react, although nitration could be achieved with the 8-methyl derivative. All four monohydroxyquinolizinium ions undergo bromination although the nature of the reactive species has not been established. Bromination of 1-hydroxyquinolizinium bromide in concentrated hydrobromic acid gives the 2-bromo derivative (129)<sup>131</sup>; bromination can occur in the 4 position if a substituent is present in position 2.<sup>12</sup> Similar bromination of the 2-,<sup>106</sup> or 3-hydroxyquinolizinium salts<sup>11</sup> gives monobromohydroxyquinolizinium salts 130 or 131. The interesting feature is the retention of the "naphthalene" pattern with no evidence of substitution in the 2 or 3 positions.

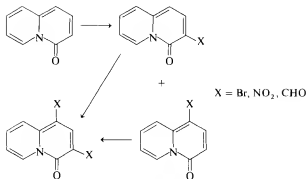


Whereas the substitution reactions with the other hydroxyquinolizinium salts have been performed under protonating conditions, and are less likely to proceed through small proportions of the quinolone or betaine form, many of the reactions of the 4-substituted compound could be viewed as addition-elimination reactions. Thyagarajan and co-workers have performed many reactions on 4-quinolizones. Bromination of the parent compound<sup>132</sup> or of the 1-formyl-,<sup>33</sup> 1-acetyl-,<sup>33</sup> or 1-ethoxycarbonyl-4-quinolizones,<sup>34</sup> leads to 3-bromo derivatives, followed in the case of the parent compound by entry of a second bromine atom in position 1. Direct nitration of 4-quinolizone gave the 1,3-dinitro-4-quinolizone.<sup>132</sup> The powerful nitronium ion was shown to displace most other groups; in increasing order of difficulty were H, CH<sub>3</sub>CO, CO<sub>2</sub>H, and Br.<sup>33</sup> Bromine could be used to displace the carboxyl group.<sup>33,34</sup> Formylation was achieved using the Vilsmeier reagent to give the 1-formyl- and the 3-formyl-4-quinolizones, as well as the 2,4-diformyl derivative,<sup>33</sup> but acetylation failed under a wide variety of conditions<sup>34</sup> (Scheme 1).

<sup>131</sup> A. Fozard and G. Jones, *J. Chem. Soc.*, 2203 (1963).

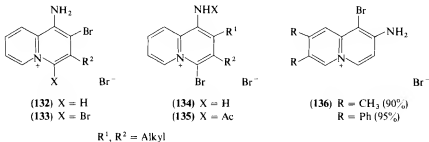
<sup>132</sup> B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **20**, 1051 (1964).





SCHEME I

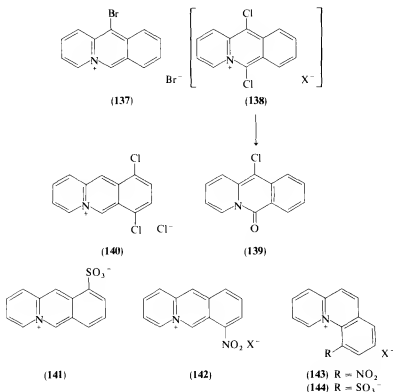
The second major group of quinolizinium salts which undergo electrophilic substitution are the amines. A 1-aminoquinolizinium salt with available bromination sites at positions 2 or 4 gave mainly the 2-bromo derivatives (**132**), with some 2,4-dibromo derivative (**133**), but no 4-bromo derivative.<sup>133</sup> However, high yields of 4-bromo-1-aminoquinolizinium salts (**134**) could be obtained from 2,3-dialkyl derivatives, and by using forcing conditions it was possible to brominate 1-acetamido-2,3-dimethylquinolizinium bromide, the least activated quinolizinium salt undergoing electrophilic substitution, to give **135**. Bromination of 2-aminoquinolizinium salts gave, as expected by analogy with the hydroxyquinolizinium salts, only the 1-bromo derivatives (**136**).



Attempts to brominate benzo[*b*]quinolizinium bromide (**3**) with liquid bromine gave an addition product (Section II.B). Bromination with bromine and aluminum bromide in dimethylformamide gave 11-bromobenzo[*b*]quinolizinium bromide (**137**).<sup>71</sup> Sulfuryl chloride and aluminum chloride under similar reaction conditions gave the chlorobenzquinolizininone (**139**), presumably from the 6,11-dichlorobenzquinolizinium salt (**138**).<sup>71</sup> Without

<sup>133</sup> T. L. Hough and G. Jones, *J. Chem. Soc.*, 1088 (1968).

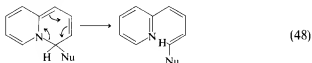
dimethylformamide, sulfonyl chloride and aluminum chloride gave 7,10-dichlorobenzo[*b*]quinolizinium salt **140**. Probably, electrophilic substitution took place in DMF; without the solvent addition-elimination occurred. There is no satisfactory explanation for the preference of halogen for the 6 and 11 positions over the less electron deficient 7 to 10 positions. Sulfonation of benzo[*b*]quinolizinium salts (**3**) gave the 10-sulfonyl betaine (**141**),<sup>118</sup> nitration the 7-nitrobenzo[*b*]quinolizinium salts (**142**).<sup>119</sup> Nitration of benzo[*c*]quinolizinium salts (**4**) gave 10-nitrobenzo[*c*]quinolizinium salts (**143**), sulfonation a betaine formulated as **144**.<sup>120</sup>



#### D. NUCLEOPHILIC SUBSTITUTION

For positively charged aromatic systems, a high degree of reactivity toward nucleophiles would be expected at the positions  $\alpha$  or  $\gamma$  to the positively charged nitrogen atom. Thus, substitution should occur at positions

2, 4, 6, and 8 in the quinolizinium salts (**1**) and a number of such substitutions are known. There are no examples of replacements on the parent quinolizinium ion where hydride ions are lost. A number of nucleophilic reagents attack position 4, giving presumably initially a 4*H*-quinolizine (Eq. 48) although these are rarely isolated (see Section IV,B for one example of hydride addition); such attack is followed by ring opening with the sole exception of borohydride reduction in protic media (Section IV,B). Such reactions with Grignard reagents, or with amines, are dealt with in Section IV,F.



Most nucleophilic substitutions require a better leaving group than hydride. Reaction of 2-bromoquinolizinium bromide (**145a**) with silver acetate gave 2-hydroxyquinolizinium bromide (**145b**) (after hydrolysis of the acetoxy derivative).<sup>106</sup> A similar reaction has been performed on 4-bromo-3-hydroxyquinolizinium bromide (**146**).<sup>11</sup> A very large number of 2-aminoquinolizinium salts (**147**) have been prepared from 2-bromo- or from 2-bromo-6-methylquinolizinium bromides, the reaction proceeding easily in boiling 2-propanol.<sup>134</sup> The amines used were primary or secondary, aliphatic or aromatic, and included some hydrazines: some were antiinflammatory and antiulcerous<sup>135-143</sup> agents, others anthelmintics.<sup>134,144,145</sup> By contrast, while 1-acetoxy-2-bromoquinolizinium bromide (**148**) was reported to give the amines (**149**) by nucleophilic substitution,<sup>146</sup> 1-hydroxy-2-bromoquinolizinium bromide (**150**) gave salts such as **151**.<sup>147</sup> The other series of nucleophilic substitutions is that reported by Leaver *et al.*<sup>148</sup> in which halide is the leaving group from 4-chloroquinolizinium perchlorate. Malonates or

<sup>134</sup> R. J. Alaïmo, C. J. Hatton, and M. K. Eckman, *J. Med. Chem.* **13**, 544 (1970).

<sup>135</sup> R. J. Alaïmo and M. M. Goldenberg, *J. Pharm. Sci.* **63**, 1939 (1974).

<sup>136</sup> R. J. Alaïmo and M. M. Goldenberg, *J. Med. Chem.* **18**, 1145 (1975).

<sup>137</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,763,174 (1973).

<sup>138</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,856,803 (1974).

<sup>139</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,856,804 (1974).

<sup>140</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,880,868 (1975).

<sup>141</sup> R. J. Alaïmo and M. M. Goldenberg, Ger. Offen. 2,339,788 [CA **80**, 133289 (1974)].

<sup>142</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,899,479 (1975).

<sup>143</sup> R. J. Alaïmo and M. M. Goldenberg, Ger. Offen. 2,239,272 [CA **78**, 136113 (1973)].

<sup>144</sup> R. J. Alaïmo, British Patent 1,170,230 (1969).

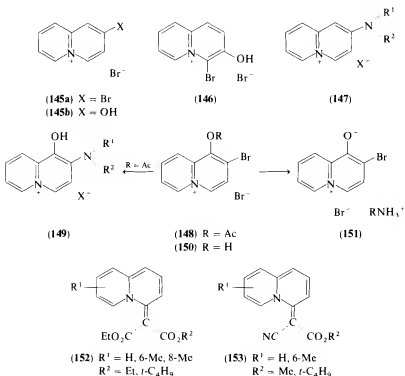
<sup>145</sup> R. J. Alaïmo, U.S. Patent 3,517,019 (1970).

<sup>146</sup> R. J. Alaïmo and M. M. Goldenberg, U.S. Patent 3,780,048 (1973).

<sup>147</sup> R. J. Alaïmo and M. M. Goldenberg, Ger. Offen. 2,521,047 [CA **84**, 121671 (1976)].

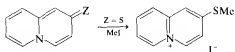
<sup>148</sup> D. F. Farquhar, T. T. Gough, and D. Leaver, *J. C. S. Perkin I*, 341 (1976).

cyanoacetates reacted in tetrahydrofuran to give the exomethylene derivatives **152** and **153**, respectively, having stereochemistry as shown.



The quinolizones can be converted by nucleophiles to halides or thiones. Thus, 2-quinolizone (**154a**) reacts with phosphoryl bromide to give 2-bromoquinolizinium bromide (**145**), and with phosphorus pentasulfide to give a thione (**154b**) converted to the 2-methylthioquinolizinium iodide (**154c**).<sup>106</sup> Many 4-quinolizones have been converted to 4-chloroquinolizinium salts by phosphoryl chloride; examples are provided by the 6-methyl and 8-methyl derivatives **155** and **156**.<sup>148</sup> In the case of 2-hydroxy-4-quinolizone (**157**), the 2-chloro compound is formed preferentially.<sup>48</sup> The 2-methylthio-4-quinolizones undergo apparent nucleophilic substitution by amines, to give 2-amino-4-quinolizones (**158**).<sup>40,42,149</sup> Active methylene derivatives can be substituted for thiomethyl groups as in the preparation of compound **159**.<sup>149</sup> Leaver *et al.*<sup>148</sup> were unable to repeat the reported

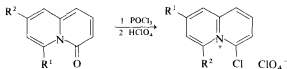
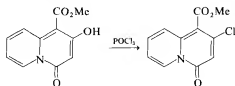
<sup>149</sup> G. Kobayashi, Y. Matsuda, and R. N. Natsuki, *Yakugaku Zasshi* **91**, 1275 (1971) [*CA* **76**, 85663 (1972)].



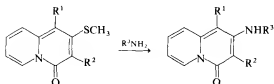
(154a) Z = O

(154b) Z = S

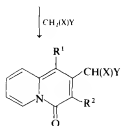
(154c)

(155) R<sup>1</sup> = Me; R<sup>2</sup> = H(156) R<sup>1</sup> = H; R<sup>2</sup> = CH<sub>3</sub>

(157)

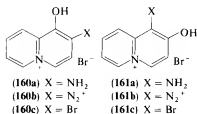


(158) R<sup>1</sup> = CN, CO<sub>2</sub>CH<sub>3</sub>, CO<sub>2</sub>Et  
 R<sup>2</sup> = 2-pyridyl, CO<sub>2</sub>R  
 R<sup>3</sup> = CH<sub>2</sub>Ph, CH<sub>2</sub>CH<sub>2</sub>OH, H  
 CH<sub>2</sub>CH<sub>2</sub>NEt<sub>2</sub>

(159) R<sup>1</sup> = CO<sub>2</sub>Et, CN; R<sup>2</sup> = CNX: H CO<sub>2</sub>Et CN CN CO<sub>2</sub>MeY: NO<sub>2</sub> CO<sub>2</sub>Me CO<sub>2</sub>Me Ph CO<sub>2</sub>Me

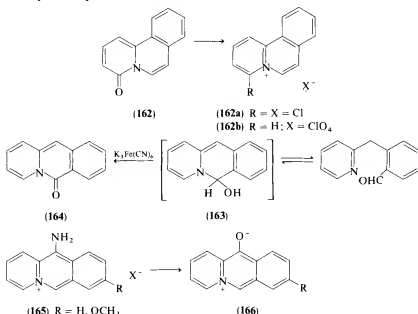
conversion of 4-methylthioquinolinolizinium iodide to the malonate (152, R<sup>1</sup> = H, R<sup>2</sup> = Et).

Simple 1-aminoquinolinolizinium salts do not form stable diazonium salts (see Section IV,F), since they undergo ring-opening reactions. The isomeric hydroxyamines **160a** and **161a** gave diazonium salts (**160b**, **161b**) (later



coupled with  $\beta$ -naphthol), and these, on heating in dimethylformamide gave the corresponding bromophenols (160c, 161c).<sup>130,150</sup>

Benzo[*a*]quinolizin-4-one (162) reacts with phosphoryl chloride to give the 4-chlorobenzoquinolizinium salt (162a), and this has been reductively dechlorinated by zinc and acetic acid to 162b.<sup>85</sup> Benzo[*b*]quinolizinium salts (3) are more reactive toward nucleophiles than the bicyclic compounds, and, for example, give directly the quinolizin-6-one (164) with alkaline ferricyanide.<sup>151</sup> In a basic medium, they are thought to be in equilibrium with the 6*H*-6-hydroxy compound (163) which in turn is in equilibrium with the bicyclic aldehyde (see Section IV.F).<sup>76</sup> The 11-aminobenzo[*b*]quinolizinium salts (165) underwent ring opening when treated with nitrous acid, but gave the 11-hydroxybenzoquinolizinium betaines (166) when treated with aqueous hydrochloric acid.<sup>77</sup>



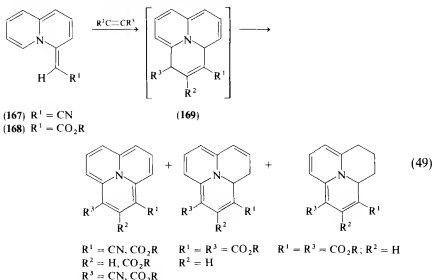
<sup>150</sup> A. Fozard and G. Jones, *J. Chem. Soc.*, 2763 (1964).

<sup>151</sup> L. A. Paquette, *Chem. Ind. (London)* **28**, 1292 (1962).

## E. CYCLOADDITION REACTIONS

There are no reported cycloadditions to bicyclic quinolizinium salts. The reactions in this section fall into two groups, cycloadditions to 4-quinolizones or related compounds and the very extensively studied "cationic polar cycloadditions" to benzo[*b*]quinolizinium salts.

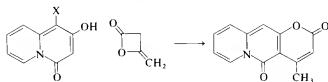
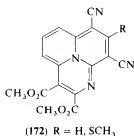
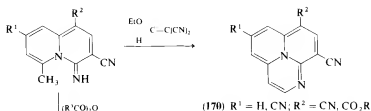
The exomethylene quinolizines **152** and **153** (Section IV,D) were converted to the monosubstituted derivatives **167** and **168**, and these reacted with acetylenes to give the cyclazines or their di- or tetrahydro derivatives (Eq. 49),<sup>148</sup> dihydrocyclazine **169** being the first addition product.



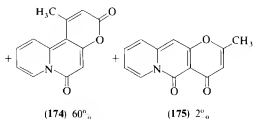
The synthesis of 4-iminoquinolizines has been mentioned (Section II,A,3). Imines with a 6-methyl group can react with an excess of ethoxymethylene malononitrile to give azacyclazines (**170**),<sup>35,36</sup> or with carboxylic acid anhydrides to give substituted azacyclazines (**171**).<sup>36,152</sup> Imines with no substituent at position 6 react with dimethyl acetylenedicarboxylate to give azacyclazines (**172**).<sup>41</sup> Diketene reacted with 2-hydroxy-4-quinolizone (**176a**) to give hydroxypyranquinolizones **173–175**.<sup>153</sup> The linear condensation product was also obtained from 2-hydroxy-4-quinolizone or from the ester (**176b**) by reaction with  $\beta$ -aminocrotonate, in the latter case after hydrolysis and decarboxylation of the intermediate.

<sup>152</sup> G. Kobayashi, Y. Matsuda, Y. Tominaga, C. Maseda, H. Awaya, and K. Kurata, *Chem. Pharm. Bull.* **23**, 2759 (1975).

<sup>153</sup> T. Kappe and Y. Linnau, *Justus Liebigs Ann. Chem.* **761**, 25 (1972).



(176a)  $X = \text{H}$   
 (176b)  $X = \text{CO}_2\text{CH}_3$



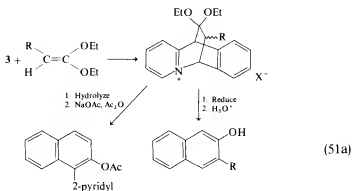
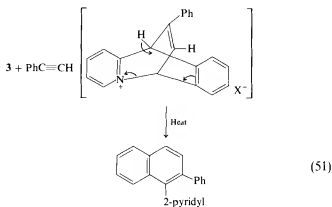
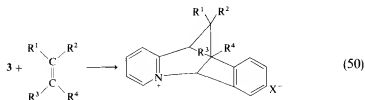
The discovery that benzo[*b*]quinolizinium salts could, like anthracene, photodimerize,<sup>154</sup> or undergo cycloaddition reactions, has led to many interesting papers. An excellent review is available for cycloaddition reactions<sup>155</sup> which occur with electron-rich rather than electron-deficient alkenes. For this reason, and because of the proposed mechanism, they

<sup>154</sup> C. K. Bradsher, L. E. Beavers, and J. H. Jones, *J. Org. Chem.* **22**, 1740 (1957).

<sup>155</sup> C. K. Bradsher, *Adv. Heterocycl. Chem.* **16**, 289 (1974).

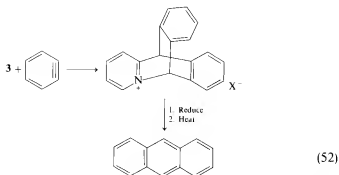


have been called "cationic polar cycloadditions." Work since 1974 will be reviewed here with reference to earlier papers for clarification only. The importance of the cycloadditions [a general formulation of which is given in Eq. (50)] lies not only in their contribution to theory, but in their use for the synthesis of naphthalenes<sup>156</sup> (Eq. 51) or naphthols<sup>157</sup> (Eq. 51a), and anthracenes (Eq. 52).<sup>157</sup>



<sup>156</sup> W. S. Burnham and C. K. Bradsher, *J. Org. Chem.* **37**, 355 (1972).

<sup>157</sup> D. L. Fields, *J. Org. Chem.* **36**, 3002 (1971).



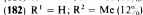
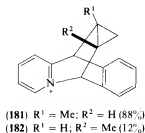
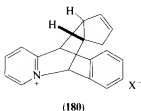
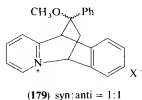
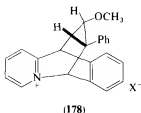
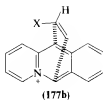
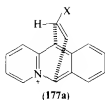
A full discussion of the mechanism of cationic polar cycloaddition has been given in a paper which reports a Hammett plot for the addition of various 9-substituted benzo[*b*]quinolizinium perchlorates to ethyl vinyl ether.<sup>155</sup> An excellent agreement was obtained using  $\sigma_p$  but poor agreement with  $\sigma_m$ . Bradsher *et al.* also observed charge transfer absorption when benzo[*b*]quinolizinium perchlorate was mixed with *N*-vinylcarbazole, and suggested that the high regioselectivity was due to a charge transfer complex with the very electron-deficient 6-position in the aromatic ion complexed to the more negatively polarized carbon atom of the double bond, as in formula 177. The high stereoselectivity with readily polarizable electron-rich alkenes was attributed to coulombic repulsion between the electron-releasing group X and the nitrogen atom of the positively charged benzo[*b*]quinolizinium ion, favoring 177a rather than 177b. Westerman and Bradsher<sup>158</sup> have reported detailed studies for syn:anti ratios in the addition of styrenes to benzo[*b*]quinolizinium salts, syn being defined relative to the benzenoid ring of the adduct. The ratios obtained seem to bear out the charge repulsion theory and varied from 93% syn for the  $\beta$ -methoxystyrene adduct (178) to approximately 50% syn for the adduct (179) from  $\alpha$ -methoxystyrene. They also studied the addition of a number of cyclic dienes, conjugated and unconjugated, noting a considerable rate enhancement for the cyclic conjugated dienes relative to the cycloalkene. The reaction with cyclopentadiene, previously reported<sup>159,160</sup> to give syn adduct 180, was contrasted with 1,3-cyclohexadiene, giving less stereoselectivity (66% syn). 1,5-Cyclooctadiene gave only syn adduct with no evidence of transannular reaction as expected for an intermediate carbocation. Other alkenes examined were cyclopropene and 1-methylcyclopropene.<sup>161</sup> Both showed high

<sup>158</sup> I. J. Westerman and C. K. Bradsher, *J. Org. Chem.* **44**, 727 (1979).

<sup>159</sup> C. K. Bradsher, F. H. Day, A. T. McPhail, and P. W. Wong, *J. C. S. Chem. Commun.*, 156 (1973).

<sup>160</sup> C. K. Bradsher and F. H. Day, *J. Heterocycl. Chem.* **10**, 1031 (1973).

<sup>161</sup> C. K. Bradsher, G. L. B. Carlson, and M. G. Adams, *J. Org. Chem.* **44**, 1199 (1979).

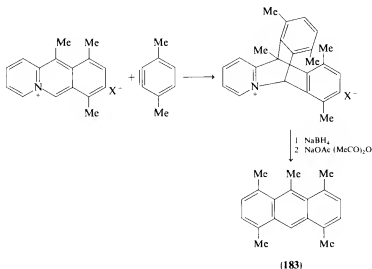


stereoselectivity to give syn adducts; the 1-methycyclopropene adduct was a mixture of two syn derivatives (**181** and **182**), (88:12).

Westerman and Bradsher<sup>162</sup> have reported a detailed examination of the regioselectivity of addition to benzo[*b*]quinolizinium salts. Almost all the additions can be explained by the "polar" model in which the alkene is joined to the most electrophilic position (6) of the benzo[*b*]quinolizinium salt by the carbon atom predicted to be most active in electrophilic additions. This "ground state" prediction, however, fails for the addition of acrylonitrile, methyl methacrylate, ethyl acrylate, and crotononitrile, although for the latter two cases a mixture of regioisomers is obtained. The frontier orbital theory has been used to explain the "anomalous" addition of acrylonitrile, the largest coefficient in the HOMO being on the  $\beta$ -carbon, which therefore bonds with the largest LUMO coefficient in the benzo[*b*]quinolizinium

<sup>162</sup> I. J. Westerman and C. K. Bradsher, *J. Org. Chem.*, **43**, 3002 (1978).

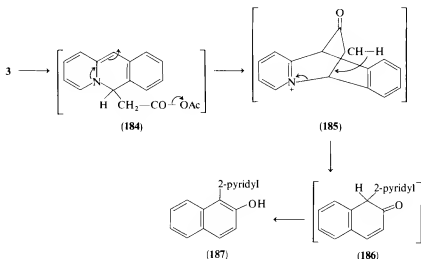
salt.<sup>163</sup> To summarize, the anomalies in regiospecificity are alkenes with electron-withdrawing polarizable groups. Other correlations which have been proposed for the cycloaddition of styrenes include a frontier orbital treatment,<sup>95</sup> and an attempt to correlate the <sup>1</sup>H-NMR shift of the 6H on the benzoquinolizinium salt with the rate of cycloaddition. Finally, it has been shown that the rate of cycloaddition increases with increasing steric strain in the benzo[*b*]quinolizinium salt.<sup>114,164</sup> Thus, an acceleration of 13.6 times was found for reaction between styrene and 11-methylbenzo[*b*]quinolizinium salts, with a further acceleration of more than ten times when 7,10,11-trimethylbenzo[*b*]quinolizinium perchlorate was used. To explain the deceleration shown by introduction of a methyl group into position 6, activation energies and entropies of activation were determined for the unsubstituted, the 11-methyl-, and the 6-methylbenzo[*b*]quinolizinium salts, and the conclusion was reached that the deceleration is due to a larger negative entropy of activation in the 6-methyl derivative, overcoming the effect of the slightly lower energy of activation. Hart *et al.*<sup>74</sup> have used the 7,10,11-trimethylbenzo[*b*]quinolizinium perchlorate in a cycloaddition with 3,6-dimethylbenzynes to produce, by Fields' method, the very hindered anthracene **183**. When benzo[*b*]quinolizinium bromide (**3**) is heated with sodium



<sup>163</sup> I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," p. 129. Wiley, New York, 1976.

<sup>164</sup> C. K. Bradsher, N. A. Porter, and T. G. Wallis, *J. Org. Chem.* **39**, 1172 (1974).

acetate and acetic anhydride the pyridylnaphthol derivative (187) is produced.<sup>165</sup> It has been suggested that the mechanism involves a two stage cycloaddition via 184 to give the bridged intermediate (185), which breaks down in accordance with Fields' mechanism via 186.



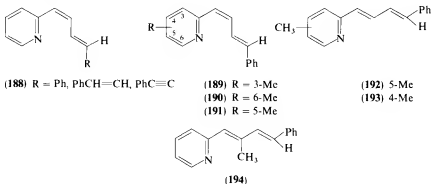
## F. RING-OPENING REACTIONS

As briefly noted in Section IV,D, nucleophilic attack on unsubstituted quinolizinium salts occurs next to the nitrogen atom, leading to a quinolizine. In the case of the bicyclic quinolizinium salts most such nucleophilic additions are followed, not by loss of hydride ion but by opening of the ring, giving a derivative of 2-pyridylbutadiene. The simplest reaction of this type is hydride reduction in nonprotic solvents.<sup>128</sup> The product with lithium aluminum hydride was unstable, but <sup>1</sup>H-NMR evidence and the observation that catalytic reduction gave 2-*n*-butylpyridine led to the formulation of the reduction product as (*Z*)-1-(2-pyridyl)buta-1,3-diene (115a). From sodium borohydride a 1-(2-pyridyl)but-2-ene (115b) was obtained. Miyadera *et al.*<sup>166</sup> also examined the reaction of quinolizinium bromide (1) with methyl-, phenyl-, cinnamyl-, and phenylethynylmagnesium halides. With methylmagnesium iodide the pyridylpentadiene was not fully characterized, but

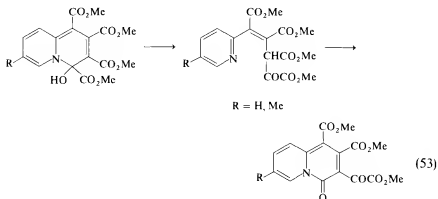
<sup>165</sup> M. Shamma, J. L. Moniot, L. A. Smeltz, W. A. Shores, and L. Toeke, *Tetrahedron* **33**, 2907 (1977).

<sup>166</sup> T. Miyadera, E. Ohki, and I. Iwai, *Chem. Pharm. Bull.* **12**, 1344 (1964).

with the other Grignard reagents the evidence was strong that the (*Z:E*)-1,3-butadiene **188** was formed. When the four monomethylquinolizinium bromides were treated with phenylmagnesium bromide the 1-methyl-, the 3-methyl- and the 4-methyl derivatives gave uniquely attack on the un-methylated rings to produce pyridylbutadienes (**189–192**).<sup>167</sup> The 2-methylquinolizinium salt gave four isomeric methylpyridylbutadienes, which on irradiation gave the two butadienes (**193** and **194**) so that in this case both rings were attacked.

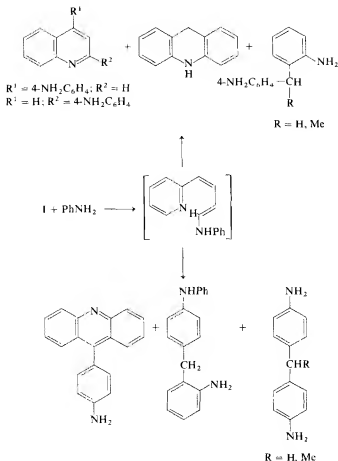


Acheson *et al.*<sup>167a</sup> found that treatment of quinolizinium 1,2,3,4-tetracarboxylates with weak aqueous base gave the quinolizones, as shown in Eq. (53), presumably via the monocyclic intermediates.



<sup>167</sup> T. Miyadera, *Chem. Pharm. Bull.* **13**, 503 (1965).

<sup>167a</sup> R. M. Acheson, D. M. Goodall, and D. A. Robinson, *J. Chem. Soc.*, 2633 (1965).

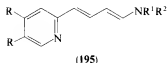


SCHEME 2

Miyadera and Tachikawa<sup>168</sup> reported that quinolizinium bromide reacted with aniline to give seven products (Scheme 2), presumably via 1-anilino-4-(2-pyridyl)butadiene, with subsequent recyclization to quinolines or loss of  $\alpha$ -picoline. Moerler and Kröhnke<sup>169</sup> were able to isolate good yields of the aminobutadienes **195** when quinolizinium salts were boiled with piperidine or morpholine. The reaction failed with 2,3,6-trimethyl- or 2,3,7-trimethyl-quinolizinium salts, presumably because of steric hindrance.

<sup>168</sup> T. Miyadera and R. Tachikawa, *Tetrahedron* **25**, 837 (1969).

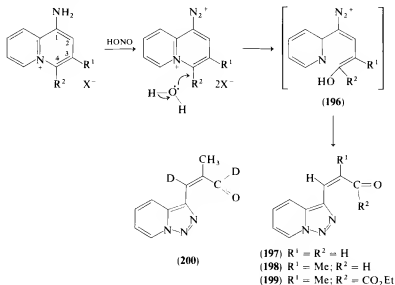
<sup>169</sup> D. Moerler and F. Kröhnke, *Justus Liebigs Ann. Chem.* **744**, 65 (1971).



R = H, Me, Ph

R¹, R² = piperidine, morpholine

When the quinolizinium salt bears a very powerful electron-withdrawing group, ring opening can occur at low temperatures in aqueous acid. Such a group is the diazonium cation, and attempts to diazotize 1-aminoquinolizinium salts led, via the ring-opened intermediate **196** to triazolo[1,5-*a*]-pyridines **197–199**.<sup>133,170,171</sup> It is noteworthy that the *Z* double bond is retained in the side chain, and that the deuterium was fully retained when a [2,4-<sup>2</sup>H<sub>2</sub>]-1-amino-3-methylquinolizinium salt was treated with nitrous acid, giving compound **200**.

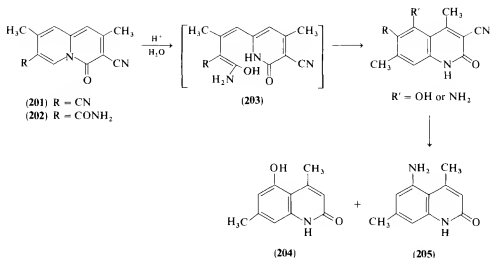


The substituted 4-quinolizones **201** and **202** are hydrolyzed by hot 80% sulfuric acid, giving presumably a pyridone (**203**) which recycles to quinolones **204** and **205**.<sup>39</sup>

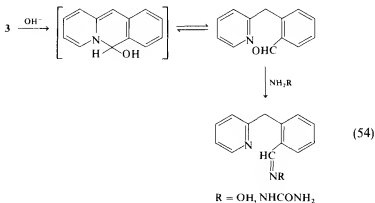
<sup>170</sup> L. S. Davies and G. Jones, *J. Chem. Soc. C*, 688 (1970).

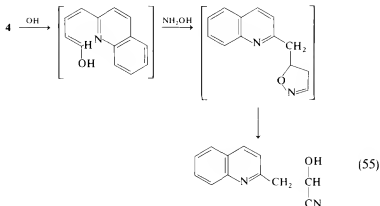
<sup>171</sup> L. S. Davies and G. Jones, *Tetrahedron Lett.*, 1549 (1969).



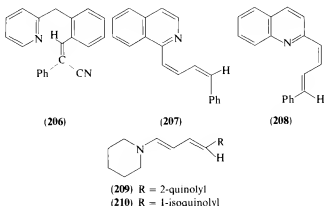


The benzoquinolizinium salts undergo broadly the same ring-opening reactions as the bicyclic system, although usually more easily. Oxidative ring opening has been mentioned (Section IV,A), in particular, its use to establish the structure of substituted benzo[*b*]quinolizinium salts by converting them to 2-(*o*-carboxybenzoyl)pyridines.<sup>11,118</sup> Benzo[*b*]quinolizinium salts (3) and benzo[*c*]quinolizinium salts (4) are unstable toward bases, the hydroxyquinolizine intermediate being in equilibrium with the ring-opened aldehyde. The aldehyde can be trapped by hydroxylamine or semicarbazide or by borohydride reduction. The sequence for the linear system is shown in Eq. (54),<sup>76</sup> for the angular system in Eq. (55).<sup>120</sup>





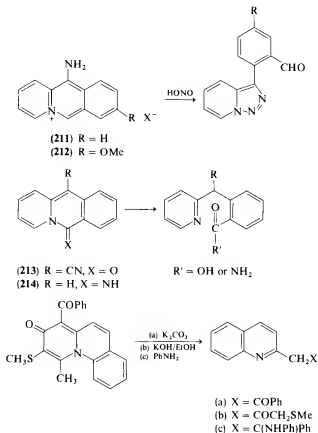
A sequence similar to Eq. (53) initiates the opening of benzo[*b*]quinolizinium salts (**3**) by sodium acetate and acetic anhydride (Section IV.E),<sup>165</sup> and the production of compound **206** from the benzo[*b*]quinolizinium ion. Benzo[*a*]quinolizinium bromide (**2**) and benzo[*c*]quinolizinium bromide (**4**) react with phenylmagnesium bromide to give the 1-phenyl-4-quinolyl or isoquinolylbutadienes **207** and **208**, respectively.<sup>172</sup> These angular polycyclic systems are also opened by piperidine, giving quinolyl- or isoquinolylbutadienes **209** or **210**. Benzo[*b*]quinolizinium salts, however, give a 6*H*-quinolizine.<sup>169</sup>



Diazotization of 11-aminobenzo[*b*]quinolizinium salts **211** and **212** leads to ring opening and formation of pyridotriazoles,<sup>77</sup> as reported for bicyclic

<sup>172</sup> R. J. Alaimo and M. M. Goldenberg, *J. Pharm. Sci.* **67**, 1183 (1978).

aminoquinolizinium salts. Alkaline hydrolysis of the cyanobenzo[*b*]quinolizin-6-one (**213**) or the imine (**214**) gives some ring-opened product.<sup>76,86</sup> The thiomethylbenzo[*c*]quinolizin-3-one (**215**) undergoes several reactions in which the "pyridone" ring is opened; these are summarized in Scheme 3.<sup>89</sup>



SCHEME 3

## V. Substituted Quinolizinium Salts

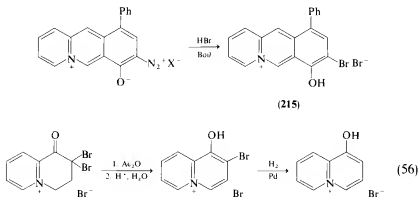
### A. ALKYL AND ARYL DERIVATIVES

All known alkyl and aryl quinolizinium salts have been produced by ring synthesis; there are no reports of direct alkylation of an already formed quinolizinium salt. Alkyl and aryl groups (2-furyl) is the only reported ex-

ample<sup>147</sup>) can be oxidized to give formyl- or carboxyquinolizinium salts; the latter readily form stable zwitterions. Only methyl groups in the 2 or 4 position of the quinolizinium salts are oxidized by selenium dioxide (Section IV,A). These methyl groups are also active in condensation.

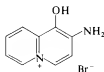
## B. HALOGENOQUINOLIZINES

Examples of fluoro-, chloro-, bromo-, and iodoquinolizinium salts are known. In most cases they have been obtained by ring synthesis of already halogenated precursors, but if sufficient activation is present bromination of bicyclic quinolizinium salts can be achieved (Section IV,C). Benzoquinolizinium salts can be halogenated on the ring remote from the positively charged nitrogen atom, possibly by an addition-elimination process (Section IV,B). The only examples of introduction of bromine via diazonium salts have been from aminohydroxyquinolizinium salts and the replacement conditions involved the heating of the bromide salt in dimethylformamide, with the bromide ion as the only source of bromine.<sup>130,150</sup> A similar preparation of a benzo[*b*]quinolizinium salt used boiling hydrobromic acid, giving compound **215**.<sup>73</sup> Hydroxyquinolizinium salts ( $\alpha$ - or  $\gamma$ - to the nitrogen atom) react with sulfuryl chloride to give chloro derivatives or with phosphorus tribromide to give bromoquinolizinium salts (Section IV,D). Bromine or chlorine in these "active" positions is readily replaced by nucleophiles (Section IV,D). The halogen can be removed reductively, by zinc and acetic acid,<sup>85</sup> or catalytically. By the latter route bromine can also be removed from the less reactive 1 position of bromohydroxyquinolizinium salts.<sup>150</sup> An example of a synthetic sequence involving reductive removal of bromine is shown in Eq. (56).<sup>131</sup>

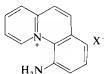


## C. NITROQUINOLIZINES

The only mononitroquinolizinium salts are the 10-nitrobenzo[*c*]- and the 10-nitrobenzo[*b*]quinolizinium derivatives.<sup>119,120</sup> In the bicyclic series nitrohydroxyquinolizinium salts have been made by direct nitration,<sup>130</sup> and nitro-4-quinolizones by nitration of 4-quinolizones, or by ring synthesis.<sup>34</sup> All these nitrations are dealt with in Section IV,C. Nitro groups have been reduced catalytically, for example, to give amines **216**<sup>130</sup> and **217**.<sup>120</sup>



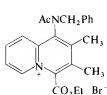
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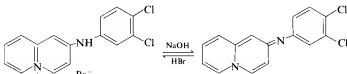
(217)

## D. AMINOQUINOLIZINIUM SALTS

Aminoquinolizinium salts have been prepared by ring synthesis (Section II,A and B), by reduction of nitroquinolizinium salts (Section V,C) and by direct nucleophilic replacement of 2-methylthio-4-quinolizones or of 2-bromoquinolizinium salts (Section IV,D). No  $pK_a$  values are available, although 2-aminoquinolizinium salts seem, qualitatively, to be weaker bases than 1- or 3-aminoquinolizinium salts. The amines can be acetylated, and the acetyl amines hydrolyzed, usually with boiling hydrobromic acid. In one case, the 1-(*N*-acetylbenzylamino)quinolizinium salt **218**, boiling hydrobromic acid removed both the benzyl and the acetyl groups.<sup>9</sup> The behavior of aminoquinolizinium salts toward nitrous acid is variable. The only stable diazonium salts are those with an adjacent hydroxyl group which might be stabilized in the diazoketone form (Section IV,D).<sup>130,150</sup> The unsubstituted 2-aminoquinolizinium ion has not been prepared; experiments with nitrous acid on alkyl substituted 2-aminoquinolizinium salts were complicated by



(218)



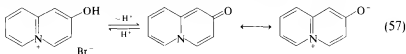
(219)

C-nitrosation or internal coupling.<sup>133</sup> On treatment with nitrous acid 1-aminoquinolizinium salts undergo rearrangement to triazolo[1,5-*a*]pyridines (Section IV.F). The secondary 2-arylaminoquinolizinium salts can be deprotonated to give 2-aryliminoquinolizines such as **219**.<sup>172,173</sup>

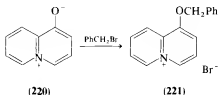
The tricyclic aminoquinolizinium salts behave similarly, forming N-acetyl derivatives,<sup>77,82,120</sup> being deprotonated to stable imines when the amine is  $\alpha$  or  $\gamma$  to the ring nitrogen atom,<sup>76,86</sup> and undergoing ring opening on attempted diazotization.<sup>77</sup> The 11-aminobenzo[*b*]quinolizinium salts give the 11-hydroxy compounds when treated with boiling hydrochloric acid.<sup>77</sup>

### E. HYDROXYQUINOLIZINIUM SALTS AND QUINOLIZONES

The four monohydroxyquinolizinium salts have been prepared, either by ring synthesis (Section I) or by modification of other substituents. They fall into two categories, the 1- and the 3-hydroxyquinolizinium salts being stronger acids ( $pK_a$  values are in Section III.A.1) than the 2- or 4-hydroxyquinolizinium salts. The weaker acids exist preferentially in the quinolizone form, the stronger acids form betaines.<sup>11</sup> The still stronger nitrohydroxyquinolizinium salts are isolated exclusively as betaines.<sup>130</sup> The full equilibrium for 2-hydroxyquinolizinium bromide<sup>106</sup> is shown in Eq. (57).



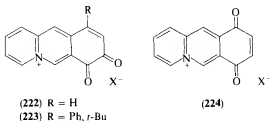
The 1- and 3-hydroxyquinolizinium salts are typical phenols, giving ferric chloride colors<sup>11,12,131</sup> and reacting with acylating agents<sup>131</sup> and, in the case of the 1-hydroxyquinolizinium betaine (**220**), alkylating agents (to give, e.g., **221**).<sup>11</sup> The 2- and the 4-quinolizones behave like pyridones, reacting with phosphorus halides to give halogenoquinolizinium salts, and with phosphorus pentasulfide to give thiones (Section IV.D). The quinolizone is stabilized toward reducing agents in the ring containing the carbonyl group, so that the pyridone structure is retained while the other ring is reduced as shown



<sup>173</sup> R. J. Alaimo, U.S. Patent 3,995,547 (1976).

by the reduction of 2-quinolizone (Section IV,B).<sup>106</sup> All the hydroxyquinolizinium salts show the expected increase in reactivity toward electrophiles, relative to the unsubstituted quinolizinium ion (Section IV,C). Infrared data suggest that the 2-hydroxy-4-quinolizone tautomer (**79**) is preferred over the 4-hydroxy-2-quinolizone (**81**).<sup>46-48</sup> Substituents in position 2 are the more readily substituted, for example, by treatment with phosphoryl chloride.<sup>48</sup>

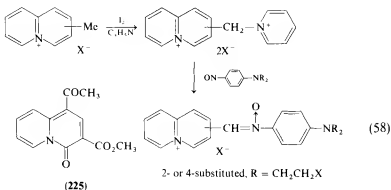
The behavior of the hydroxybenzoquinolizinium salts is similar to that of the bicyclic compounds, though most of the "phenolic" substituents reported were on the benzene ring remote from the bridgehead nitrogen atom. They were produced by ring syntheses, starting from suitably substituted phenol acetates or phenolic ethers. Protecting groups are sometimes removed<sup>73</sup> during or after cyclization by concentrated hydrobromic acid.<sup>78,79</sup> The benzoquinolizinsones reported are the benzo[*a*]quinolizin-4-one,<sup>85</sup> benzo[*b*]quinolizin-6-ones,<sup>76,86,151</sup> and benzo[*c*]quinolizin-1-,<sup>37,38,84,88</sup> and -3-ones.<sup>89</sup> The only quinones reported are the 7,8- and the 7,10-benzo[*b*]quinoliziniumquinone salts (**222**, **223**, and **224**), prepared by nitric acid oxidation of the corresponding diols.<sup>73</sup> A betaine is formed from 11-hydroxybenzo[*b*]quinolizinium salts; the phenol does not react with phosphoryl chloride and phosphorus pentachloride.<sup>77</sup>



## F. QUINOLIZINE ALDEHYDES AND KETONES

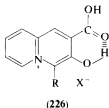
Quinolizone ketones are obtained in some ring syntheses; 3-acetyl-2-quinolizone,<sup>28</sup> and the 4-quinolizone **225**<sup>31</sup> provide examples where the ketone was in the acyclic component (acetylacetylene) and in the pyridine component (2-pyridylacetone), respectively. Aldehyde groups have been produced by direct substitution of 4-quinolizone with the Vilsmeier reagent<sup>33</sup> (acylation could not be achieved<sup>34</sup>) and by oxidation of a 2-methylquinolizinium salt with selenium dioxide.<sup>9</sup> Nitrones have been prepared by the sequence shown in Eq. (58).<sup>174</sup> Virtually no reactions of the aldehydes or ketones are reported, except their ready replacement by nitro groups in the 1-acetyl- and 3-acetyl- or -formyl-4-quinolizones.<sup>33,34</sup>

<sup>174</sup> W. Schulze and H. Willitzer, *J. Prakt. Chem.* **27**, 306 (1965).



### G. QUINOLIZINE CARBOXYLIC ACIDS AND DERIVATIVES

Many of the syntheses of quinolizones lead to ethoxycarbonyl- or cyano-substituted derivatives (Section II).<sup>29,30,33,34,84</sup> Similarly the syntheses of 2-quinolizones can provide a 1-cyano or 1-alkoxycarbonyl derivative.<sup>24,25</sup> Two syntheses have been reported in which an alkoxycarbonyl group is lost. Westphal *et al.*<sup>8</sup> condensed  $\alpha$ -diketones with 1-ethoxycarbonylmethyl-2-methylpyridinium salts and found that the alkoxycarbonyl group was lost during the reaction; Hough and Jones<sup>9</sup> provided some examples where the ethoxycarbonyl group was retained, being subsequently removed by boiling acetic anhydride or hydrobromic acid (Section II.A). Kappe<sup>46</sup> reported that in the synthesis of 2-hydroxy-4-quinolizone a methoxycarbonyl group was lost. Heating 1-methoxycarbonyl-2-hydroxy-4-quinolizone under the conditions of the synthesis did not cause loss of the ester group. Carboxyl substituted quinolizinium salts have also been prepared by oxidation of methyl<sup>9</sup> or furyl<sup>117</sup> groups. Most other preparations have involved trivial modification, usually hydrolysis of esters,<sup>25,33,34,46</sup> amides,<sup>24</sup> or nitriles.<sup>24,25,86</sup> Quinolizinium-2-carboxylic acid salts are readily converted to the zwitterion form<sup>9,117</sup>; Casini *et al.*<sup>15,175</sup> have prepared a number of hydroxycarboxylic acids of general formula **226** and studied the various degrees of ionization by <sup>1</sup>H-NMR.



<sup>175</sup> G. Casini and F. Liberatore, *Chim. Ind. (Milan)* **49**, 288 (1967).



The other major reaction is decarboxylation. A carboxyl group in position 4 is particularly easy to remove; for example, attempts to oxidize 4-methylquinolizinium bromide with selenium dioxide gave the unsubstituted quinolizinium bromide.<sup>9</sup> Decarboxylation of the 2-carboxylic acid was much more difficult, giving only a small yield of decarboxylated material after a long time in boiling quinoline. The 1- or 3-carboxy-4-quinolizones are readily decarboxylated by heating, by treatment with bromine or nitric acid,<sup>33,34</sup> and by boiling hydrochloric or hydrobromic acids. The latter conditions are used to remove ester groups in the synthesis of 4-quinolizone itself.<sup>30</sup>

## H. SULFUR DERIVATIVES

Two types of sulfur derivatives have been reported, the thiones or related thiols and their methyl ethers, and sulfonic acids. Quinolizin-2-thione<sup>106</sup> and -4-thione<sup>176</sup> have been obtained from the corresponding quinolizones by treatment with phosphorus pentasulfide; both are methylated by methyl iodide. A benzo[*c*]quinolizin-1-thione has been prepared by a ring synthesis from diphenylcyclopropenethione (Section II,B).<sup>87</sup> Other methylthioquinolizine derivatives<sup>40-42</sup> and a methylthiobenzo[*c*]quinolizin-3-one<sup>89</sup> have been synthesized. The methylthio group is replaceable by nucleophilic reagents such as amines (Section IV,D).<sup>42</sup> Benzo[*b*]- and benzo[*c*]quinolizinium sulfonic acid betaines have been prepared by direct sulfonation<sup>118,120</sup> or by ring synthesis.<sup>70</sup>

<sup>176</sup> V. Boekelheide and W. G. Gall, *J. Org. Chem.* **19**, 499 (1954).

## 1,2-Dithiole-3-thiones and 1,2-Dithiol-3-ones

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**I. Introduction**

1,2-Dithiole-3-thiones and 1,2-dithiol-3-ones will not be treated in separate sections in this survey, as very few papers dealing with 1,2-dithiol-3-ones

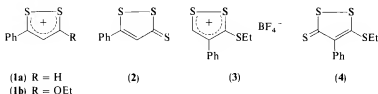
exclusively have been published. This chapter will deal with the literature published in the period 1965–1980. The literature has been reviewed until 1965 by Landis,<sup>1</sup> and until about 1970 by Vasil'eva *et al.*<sup>2</sup> in a consideration of four and five-membered cyclic disulfides. Earlier literature may also be found in Refs. 3 and 4. For a more detailed discussion of physicochemical properties of 1,2-dithiole derivatives,<sup>5</sup> Patents are included only if they involve new methods or applications.

## II. Synthesis

### A. FROM SYSTEMS CONTAINING THE 1,2-DITHIOLE RING

The trivial transformation of 1,2-dithiol-3-ones into 1,2-dithiole-3-thiones by means of phosphorus pentasulfide and analogous sulfurating agents will not be treated in this section.

Often 1,2-dithiole-3-thiones are formed as by-products in reactions involving 1,2-dithiolylum salts, probably by reaction of the 1,2-dithiolylum ion with elemental sulfur from decomposition of the dithiolylum salt. With tertiary amines, 1,2-dithiolylum salts give not tetrathiafulvalenes but 1,2-dithiole-3-thiones<sup>6</sup> (e.g., **1a** → **2**).



The reaction of elemental sulfur in pyridine with 1,2-dithiolylum salts has been used for the synthesis of several 1,2-dithiole-3-thiones.<sup>7</sup> 3-Chloro-1,2-dithiolylum salts give 1,2-dithiole-3-thiones with sulfur-free bases such as ethanol, ammonia, methyl- and dimethylamine, piperidine, morpholine, and the azide ion.<sup>8</sup> These salts form 1,2-dithiol-3-ones with carboxylic acids.<sup>8</sup>

<sup>1</sup> P. Landis, *Chem. Rev.* **65**, 237 (1965).

<sup>2</sup> T. P. Vasil'eva, M. G. Lin'kova, and O. V. Kil'disheva, *Usp. Khim.* **45**, 1269 (1976).

<sup>3</sup> N. Lozac'h and J. Vialle, *Chem. Org. Sulfur Comp.* **2**, 257 (1966).

<sup>4</sup> D. S. Breslow and H. Skolnik, in "The Chemistry of Heterocyclic Compounds, Multi-Sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles" (A. Weissberger, ed.), Part One, p. 347. Wiley, New York, 1966.

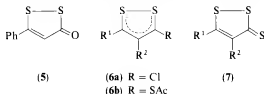
<sup>5</sup> C. T. Pedersen, *Sulfur Rep.* **1**, 1 (1980).

<sup>6</sup> H. Prinzbach, E. Futterer, and A. Lüttringhaus, *Angew. Chem.* **78**, 492 (1966).

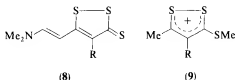
<sup>7</sup> U.S. Patent 3,225,062, [*CA* **66**, 10921 (1967)], Dec. 21, 1965.

<sup>8</sup> J. Faust, H. Spies, and R. Mayer, *Z. Chem.* **7**, 275 (1967).

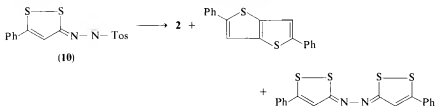
3-Ethylthio-1,2-dithiolylum fluoborates react with sulfur and form 5-ethylthio-1,2-dithiole-3-thiones<sup>9</sup> (e.g., **3** → **4**). With water–pyridine mixtures the analogous 3-ethoxy-1,2-dithiolylum salts (**1b**) give a mixture of 1,2-dithiole-3-thiones (**2**) and 1,2-dithiol-3-ones<sup>9</sup> (**5**). The reaction of 3-chloro-1,2-dithiolylum chlorides (**6a**) with thioacetic acid results in 1,2-dithiole-3-thiones (**7**) probably via a 3-acylthio-1,2-dithiolylum salt (**6b**).<sup>10</sup>



5-(2-*N,N*-Dimethylaminovinyl)-1,2-dithiole-3-thiones (**8**) have been prepared from 3-methylthio-1,2-dithiolylum salts (**9**) and *N,N*-dimethylthioformamide.<sup>11</sup>



The Stevens–Bamford reaction of 1,2-dithiol-3-one tosylhydrazone (**10**) did not give rise to 1,2-dithiolyl carbenes or species derived from these, but among other products, to 1,2-dithiole-3-thiones.<sup>12</sup>



With aryl amines the reaction of 3-methylthio-1,2-dithiolylum salts (**11**) not substituted in the 5-position gives 1,2-dithiole-3-thiones arylated in the 5-position<sup>13</sup> (**12**).

<sup>9</sup> C. Bouillon and J. Vialle, *Bull. Soc. Chim. Fr.*, 4560 (1968).

<sup>10</sup> G.-J. Wentrup, M. Koepke, and F. Boberg, *Synthesis*, 525 (1975).

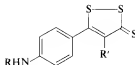
<sup>11</sup> C. Metayer, G. Duguay, and H. Quiniou, *Bull. Soc. Chim. Fr.*, 4576 (1972).

<sup>12</sup> H. Behringer and E. Meinetsberger *Tetrahedron Lett.*, 1915 (1973).

<sup>13</sup> G. Le Coustumer and Y. Mollier, *C. R. Hebd. Seances Acad. Sci., Ser. C* **274**, 1215 (1972).



(11)



(12)

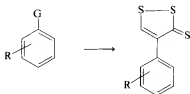
## B. FROM SYSTEMS NOT CONTAINING THE 1,2-DITHIOLE RING

### 1. From Carbohydrides

a. *Alkanes*. Syntheses starting with the reaction of alkenes with sulfur are treated in a separate section, although the primary process is probably a dehydrogenation of the alkane with formation of an alkene. No systematic studies of reaction mechanisms have been carried out. Mechanisms have been discussed in connection with general discussions of the reaction of sulfur with organic compounds.<sup>14,15</sup>

The synthesis has been demonstrated chiefly with aromatic compounds of the isopropyl benzene type (13). In some cases the alkane is used as the solvent, in other cases chlorobenzene and *o*-dichlorobenzene have been used.

A great variety of catalysts have been employed; *sym*-diphenylguanidine, mercury acetamide, mercaptobenzothiazole, mercaptobenzothiazole + ZnO are among the most used. Voronkov and Lapina have studied a series of catalysts.<sup>16</sup> Further examples are given.<sup>17-20</sup>



(13) G = isopropyl

(14) G = 2-propenyl

(15)

<sup>14</sup> R. Mayer, in "Organic Chemistry of Sulfur" (S. Oae, ed.), p. 33, Plenum, New York, 1977.

<sup>15</sup> M. G. Voronkov, "Reaktsii Sery s Organiches Kimi Soedinenijam," Nauka, Novosibirsk, 1979 (in Russian).

<sup>16</sup> M. G. Voronkov and T. V. Lapina, *Khim. Geterosikl. Soedin.* **1**, 342 (1965).

<sup>17</sup> M. G. Voronkov and T. V. Lapina, *Khim. Seraorg. Soedin., Soderzh. Neftnykh Nefteprod.* **9**, 240 (1972).

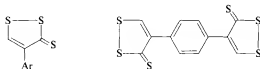
<sup>18</sup> M. G. Voronkov, T. V. Lapina, and Z. H. Minkina, *Khim. Geterosikl. Soedin.* **7**, 999 (1971).

<sup>19</sup> USSR Patent 186,458 [CA **66**, 115701 (1967)], Oct. 3, 1966.

<sup>20</sup> Ger. Offen. 2,428,876 [CA **82**, 173417 (1975)], Jan. 30, 1975.

b. *Alkenes*. As mentioned in the previous section the real starting compound in the reaction of alkanes with sulfur is probably the corresponding alkene. Consequently, many syntheses start with alkenes, usually a 2-phenyl-1-propene (**14**) to give aryl derivative **15** but the reaction has also been used for the synthesis of aliphatic-substituted compounds as well as the unsubstituted 1,2-dithiole-3-thione. The same catalysts mentioned in *1a* are favored.<sup>16</sup>

The reaction is normally carried out in a high-boiling solvent, e.g., mesitylene<sup>21,22</sup> and sulfolane.<sup>23</sup> In many cases the starting alkene is used as a solvent as in the synthesis of the two naphthyl-substituted compounds **16**<sup>24</sup>; further examples are described in patents.<sup>25,26</sup>



(16) Ar = 1- or 2-naphthyl

(17)

The reaction has also been realized in the gas phase with sulfur being generated by mixing sulfur dioxide with hydrogen sulfide.<sup>27,28</sup> This method seems to be very efficient for the preparation of aromatic and aliphatic compounds as well as the unsubstituted 1,2-dithiole-3-thione. More complex 1,2-dithiole-3-thiones such as **17** have also been prepared.<sup>28</sup> 4-Neopentyl-5-*t*-butyl-1,2-dithiole-3-thione has been prepared from triisobutylene and sulfur.<sup>29</sup> 1-Phenyl-1-propene does not give a simple thione in the reaction with sulfur, but thiol **18**. The yield was raised by the presence of hydrogen sulfide and benzoyl peroxide.<sup>30</sup>

The same result could be obtained with 2-phenyl-1-propene, which gave the 5-mercapto-substituted compound without solvent.<sup>30</sup> The reaction has also been realized with dimethylformamide as solvent.<sup>31</sup>

<sup>21</sup> E. Klingsberg, *Synthesis*, 213 (1971).

<sup>22</sup> U.S. Patent 4,116,812 [CA **90**, 57733 (1979)].

<sup>23</sup> U.S. Patent 3,847,943 [CA **82**, 57670 (1975)]. Nov. 12, 1974.

<sup>24</sup> K. Adachi and J. Tanaka, *Nippon Kagaku Kaishi*, 1666 (1978).

<sup>25</sup> Ger. Offen. 2,430,802 [CA **82**, 156258 (1975)]. Jan. 16, 1975.

<sup>26</sup> Japan Kokai 52,768 [CA **79**, 137118 (1973)]. Jul. 24, 1973.

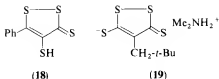
<sup>27</sup> Netherlands Patent Appl. 6,604,093 [CA **66**, 37909 (1967)]; Sept. 30, 1966. Ger. Offen. 1,275,068 [CA **69**, 86999 (1968)]. Aug. 14, 1968.

<sup>28</sup> German Patent 2,430,802 [CA **82**, 156258 (1975)]. Jan. 16, 1975.

<sup>29</sup> T. A. Burtseva, I. E. Vinogradova, A. F. Plate, and T. A. Danilova, *Khim. Tekhnol. Topl. Masel* **10**, 34 (1965).

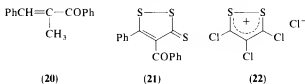
<sup>30</sup> A. Grandin, C. Bouillon, and J. Vialle, *Bull. Soc. Chim. Fr.*, 4555 (1968).

<sup>31</sup> French Patent 1,442,450 [CA **67**, 82205 (1967)]. June 17, 1966.

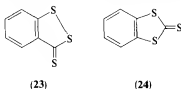


Brown has studied the thiation of alkenes in dimethylformamide in detail using both aromatic and aliphatic substituted alkenes. In all cases dimethylammonium salts of the thiolate were isolated<sup>32</sup> (e.g., **19**). Sulfuration of aroyl-substituted ethylenes results in aroyl-substituted 1,2-dithiole-3-thiones<sup>33,34</sup> (e.g., **20** → **21**).

Sulfuration of perchloropropene did not give the 1,2-dithiole-3-thione but the 3,4,5-trichloro-1,2-dithiolylium chloride (**22**).<sup>35</sup>



c. *Benzynes*. Both 1,2-benzodithiolethione (**23**) and 1,3-benzodithiolethione (**24**) are formed when a mixture of carbon disulfide and phthalic anhydride is passed through a tube filled with Vycor chips at 700°C.<sup>36,37</sup> Under the same conditions 4-chlorophthalic anhydride and trimellitic anhydride gave the corresponding substituted benzodithiolethiones.



## 2. From Ketones and Aldehydes

One of the most versatile methods for the synthesis of 5-substituted 1,2-dithiole-3-thiones is the reaction of  $\alpha$ -methylene groups of ketones with base

<sup>32</sup> J. P. Brown, *J. Chem. Soc., C*, 1077 (1968).

<sup>33</sup> J. Teste and R. Lefevre, *Bull. Soc. Chim. Fr.*, 258 (1966).

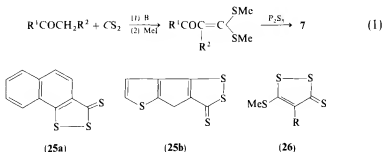
<sup>34</sup> M. Cadec, C. Trebaul, and J. Teste, *Bull. Soc. Chim. Fr.*, 2964 (1968).

<sup>35</sup> F. Boberg, R. Wiedermann, and J. Kresse, *J. Labelled Compd.* **10**, 297 (1974).

<sup>36</sup> E. K. Fields and S. Meyerson, *Tetrahedron Lett.*, 629 (1970).

<sup>37</sup> U.S. Patent 3,818,041 [*CA* **81**, 120599 (1974)], June 18, 1974.

and carbon disulfide<sup>38</sup> (Eq. 1). Further examples have been described.<sup>39-43</sup> The method has been used for the synthesis of the tricyclic systems **25a**<sup>44</sup> and **25b**.<sup>45</sup>



Aryl-substituted ketones react directly with elemental sulfur in hexamethylphosphorus triamide with formation of 1,2-dithiole-3-thiones.<sup>46,47</sup> Aryl-substituted acetaldehydes can condense likewise with carbon disulfide to give the analogous 4-aryl-substituted 1,2-dithiole-3-thiones.<sup>48</sup> The same reaction was observed with aryl-substituted acetic acid esters, in which a methylthio group is incorporated into the reaction product (**26**).<sup>49</sup> Thioketones and enthiols react analogously.<sup>50,51</sup>

The parent 1,2-dithiole-3-thione (**27**) has been prepared from the tetramethyl acetal of malondialdehyde and phosphorus pentasulfide.<sup>52</sup> In the presence of ammonia the reaction of cyclohexanone or cycloheptanone with carbon disulfide and sulfur gives as by-products the condensed 1,2-dithiole-3-thiones **28a** and **28b**, respectively.<sup>53</sup>

<sup>38</sup> A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.*, 2187 (1962).

<sup>39</sup> J. Brelivet and J. Teste, *C. R. Hebd. Seances Acad. Sci., Ser. C* **263**, 495 (1966).

<sup>40</sup> J.-P. Pradère and H. Quiniou, *C. R. Hebd. Seances Acad. Sci., Ser. C* **273**, 1013 (1971).

<sup>41</sup> A. Marci and M. M. A. El-Sukkary, *U. A. R. J. Chem.* **14**, 111 (1971).

<sup>42</sup> German Patent 1,275,068 [*CA* **69**, 86999 (1968)], Aug. 14, 1969.

<sup>43</sup> U.S. Patent 3,394,146 [*CA* **69**, 67362 (1968)], Jul. 23, 1968.

<sup>44</sup> E. Klingsberg, *J. Org. Chem.* **37**, 3226 (1972).

<sup>45</sup> Y. Poirier, L. Legrand, and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1054 (1966).

<sup>46</sup> J. Perregaard, I. Thomsen, and S.-O. Lawesson, *Acta Chem. Scand., Ser. B* **B29**, 538 (1975).

<sup>47</sup> J. Perregaard, I. Thomsen, and S.-O. Lawesson, *Acta Chem. Scand., Ser. B* **B29**, 599 (1975).

<sup>48</sup> M. Saquet and A. Thuillier, *Bull. Soc. Chim. Fr.*, 1582 (1966).

<sup>49</sup> M. Marceau and A. Thuillier, *C. R. Hebd. Seances Acad. Sci., Ser. C* **262**, 147 (1966).

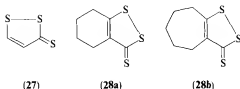
<sup>50</sup> R. Couturier, D. Paquer, and A. Thuillier, *C. R. Hebd. Seances Acad. Sci., Ser. C* **270**, 1878 (1970).

<sup>51</sup> R. Couturier, D. Paquer, and A. Vibet, *Bull. Soc. Chim. Fr.*, 1670 (1975).

<sup>52</sup> E. Meinetsberger, A. Schöffler, and H. Behringer, *Synthesis*, 802 (1977).

<sup>53</sup> T. Takeshima, K. Tazaki, N. Fukada, and M. Muraoka, *J. Chem. Res., Synop.*, 410 (1979).

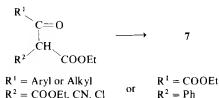




$\omega$ -Substituted propiophenones when converted to Mannich bases and  $\omega$ -chloropropiophenone give 5-aryl-substituted 1,2-dithiole-3-thiones with sulfur and morpholine.<sup>54</sup>

### 3. From $\beta$ -Ketoesters and Related Compounds

The sulfuration of  $\beta$ -ketoesters with phosphorus pentasulfide alone or in a mixture with elemental sulfur is a general method for the synthesis of 1,2-dithiole-3-thiones.<sup>4</sup> Functional groups are introduced by means of  $\beta$ -ketoesters substituted with such groups. In this way 1,2-dithiole-3-thiones substituted with chloro, cyano, and ester groups in the 4-position<sup>55</sup> and ester groups in the 5-position have been prepared<sup>56</sup> (Scheme 1).



SCHEME 1

A series of 1,2-dithiole-3-thiones substituted with nitrogen-containing heterocyclic groups has been prepared for pharmaceutical studies. Groups include pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, morpholinyl, and pyrrolidinyl.<sup>57-60</sup> The dimer of *p*-methoxyphenylthionophosphine sulfide (**29**) has been shown to be a versatile reagent for the sulfuration of  $\beta$ -ketoesters.<sup>61</sup> High yields of 1,2-dithiole-3-thiones are obtained. However, the method seems to be most suitable for small scale preparations (0.1 mol).<sup>62</sup> Keto-

<sup>54</sup> G. Purello, *Gazz. Chim. Ital.* **96**, 1078 (1966).

<sup>55</sup> C. Trebaul and J. Teste, *Bull. Soc. Chim. Fr.*, 2456 (1969).

<sup>56</sup> C. Trebaul, *Bull. Soc. Chim. Fr.*, 721 (1973).

<sup>57</sup> Ger. Offen. 2,705,641 [*CA* **87**, 152171 (1977)]. Aug. 11, 1977.

<sup>58</sup> Belgian Patent 851,262 (1977). Aug. 9, 1977.

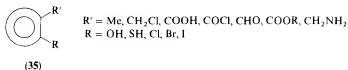
<sup>59</sup> Ger. Offen. 2,627,211 [*CA* **86**, 121373 (1977)]. Dec. 30, 1976.

<sup>60</sup> U.S. Patent 4,110,450 [*CA* **90**, 121574 (1979)].

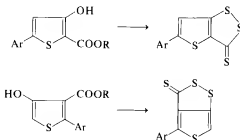
<sup>61</sup> B. S. Pedersen and S.-O. Lawesson, *Tetrahedron* **35**, 2433 (1979).

<sup>62</sup> C. T. Pedersen, unpublished results.



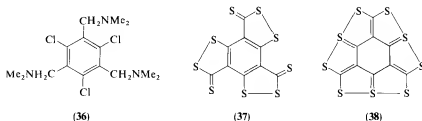
4. From *o*-Hydroxyacids and Related Compounds

Reaction of ortho-disubstituted aromatic compounds **35** with sulfuring agents gives rise to 1,2-dithiole-3-thiones where the dithiole nucleus is condensed with the aromatic ring.<sup>66-70</sup> For example, the two thiophene derivatives in Scheme 2 give rise to two isomeric 1,2-dithiole-3-thiones.<sup>71</sup>



SCHEME 2

The reaction of **36** with sulfur in dimethylformamide gave a compound which was originally ascribed the 1,2-dithiole-3-thione structure **37**.<sup>72</sup> X-Ray studies, however, showed that the coronenelike trithiapentalene structure



<sup>66</sup> S. Palazzo and L. I. Ciannola, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* **32**, 21 (1971).

<sup>67</sup> J. P. Brown and M. Thompson, *J. C. S. Perkin I*, 863 (1974).

<sup>68</sup> M. G. Voronkov and L. N. Khokhlova, *Zh. Org. Khim.* **10**, 811 (1974).

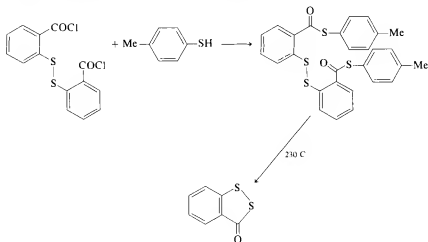
<sup>69</sup> British Patent 1,391,679 [*CA* **83**, 97260 (1975)], Apr. 23, 1975.

<sup>70</sup> Ger. Offen. 2,460,783 [*CA* **85**, 123899 (1976)], Jul. 1, 1976.

<sup>71</sup> J. Brelivet, P. Appriou, and J. Teste, *C. R. Hebd. Seances Acad. Sci., Ser. C* **269**, 398 (1969).

<sup>72</sup> J. P. Brown and T. B. Gay, *J. C. S. Perkin I*, 866 (1974).

**38** was a better representation.<sup>73</sup> Praefcke and co-workers have prepared 1,2-benzodithiolone by thermolysis<sup>74</sup> (Scheme 3).



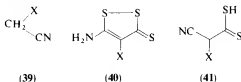
SCHEME 3

### 5. Miscellaneous

Methods not directly related to those already discussed are now considered. Pathways generally have not been studied systematically and may only be useful for the synthesis of the compound described. In some cases the yield of the desired product is so low that the compound has to be considered a by-product.

In several cases the reaction of carbon disulfide and sulfur with nitriles gives amino-substituted 1,2-dithiole-3-thiones (e.g., **39** → **40**). Malononitrile reacts in this way.<sup>75</sup>

1,2-Dithiole-3-thiones (**40**) have been prepared from  $\alpha$ -cyanodithiocarboxylates (**41**) with hydrogen sulfide.<sup>76</sup>



<sup>73</sup> L. K. Hansen and A. Hordvik, *J. C. S. Chem. Commun.*, 800 (1974).

<sup>74</sup> B. Kohne, K. Praefcke, and C. Weichsel, *Phosphorus Sulfur* **7**, 211 (1979).

<sup>75</sup> T. Takeshima, M. Yokoyama, N. Fukada, and M. Akano, *J. Org. Chem.* **35**, 2438 (1970).

<sup>76</sup> M. Yokoyama, *Bull. Chem. Soc. Jpn.* **43**, 2938 (1970).

Nitriles with an activated methylene group in the  $\alpha$ -position (**39**) react with sulfur and carbon disulfide.<sup>77</sup> Ketimines (**42**) also give 1,2-dithiole-3-thiones (**7**) with sulfur and carbon disulfide.<sup>78</sup> *N*-Aryl-3,3-bis(methylthio)-2-aryl propenimines (**43**) react with hydrogen sulfide<sup>79</sup> to give aryl product **15**.



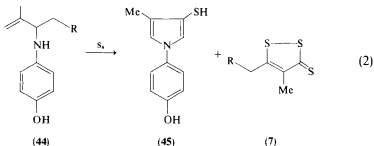
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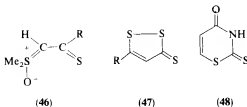
(43)

Enamines give 1,2-dithiole-3-thiones with carbon disulfide and sulfur.<sup>80</sup>

The reaction of aniline (**44**) described in Eq. (2) gives 1,2-dithiole-3-thiones (**7**) as by-products along with pyrrole (**45**).<sup>81</sup>



$\alpha$ -Thiocarbonyl dimethyloxosulfonium ylids (**46**) react with carbon disulfide and form 1,2-dithiole-3-thiones (**47**).<sup>82</sup> The parent 1,2-dithiole-3-thione (**27**) can be prepared from thiazine (**48**).<sup>83</sup>



(46)

(47)

(48)

<sup>77</sup> K. Gewald, *J. Prakt. Chem.*, **31**, 214 (1966).

<sup>78</sup> R. Mayer, H.-J. Hartmann, and J. Jentzsch, *J. Prakt. Chem.*, **31**, 312 (1966).

<sup>79</sup> C. Paulmier, Y. Mollier, and N. Lozac'h, *Bull. Chem. Soc. Fr.*, 2463 (1965).

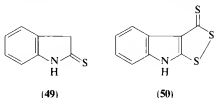
<sup>80</sup> German Patent 1,230,808 [*CA* **66**, 46420 (1967)], Dec. 22, 1966.

<sup>81</sup> I. R. Gelling and M. Porter, *Tetrahedron Lett.*, 3089 (1975).

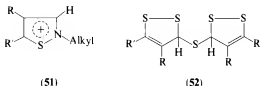
<sup>82</sup> H. Yoshida, T. Yao, T. Ogata, and S. Inokawa, *Bull. Chem. Soc. Jpn.*, **49**, 3128 (1976).

<sup>83</sup> R. N. Warren and E. N. Cain, *Chem. Ind. (London)*, 289 (1966).

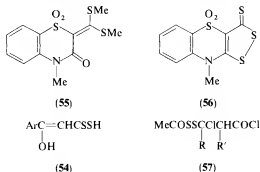
Thioxindole (49) reacted with carbon disulfide in the presence of a strong base and yielded a condensed 1,2-dithiole-3-thione (50).<sup>84</sup>



1,2-Dithiole-3-thiones were found to be formed in the reaction of *N*-alkyl isothiazolium salts (51) with hydrogen sulfide<sup>85</sup> (e.g., 51 → 52 + 7).



In reaction with aryl amines, aroyldithioacetic acids (54) gave 1,2-dithiole-3-thiones (47) in low yields.<sup>86</sup> With phosphorus pentasulfide, benzothiazinone oxide 55 gave a condensed 1,2-dithiole-3-thione 56.<sup>87</sup>



Upon pyrolysis the disulfide 57 gave 1,2-dithiol-3-ones in 70–80% yield.<sup>88</sup>  $\alpha$ -Chlorocumene reacts with sulfur in the same way as cumene (13) does.<sup>89</sup>

<sup>84</sup> G. Kobayashi, S. Furukawa, Y. Matsuda, and R. Natsuki, *J. Pharm. Soc. Jpn.* **90**, 132 (1970).

<sup>85</sup> D. M. McKinnon and M. E. Hassan, *Can. J. Chem.* **51**, 3081 (1973).

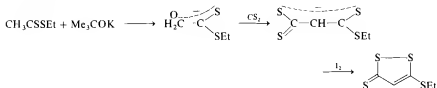
<sup>86</sup> F. Clesse and H. Quiniou, *Bull. Soc. Chim. Fr.*, 581 (1973).

<sup>87</sup> F. Eiden and F. Meinel, *Arch. Pharm. (Weinheim, Ger.)* **312**, 302 (1979).

<sup>88</sup> T. P. Vasil'eva, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 700 (1974).

<sup>89</sup> M. G. Voronkov, T. V. Lanina, A. S. Saritkov, M. I. Solov'eva, and L. I. Dubro, *Khim.-Farm. Zh.* **11**, 18 (1967).

5-Ethylthio-1,2-dithiole-3-thione has been prepared via the sequence in Scheme 4.<sup>90</sup>



SCHEME 4

### III. Reactions

#### A. METAL COMPLEXES

Complex formation between metals and 1,2-dithiole-3-thiones has long been known. The mercury(II) complex is often used for purification of 1,2-dithiole-3-thiones.<sup>1</sup>

Petillon *et al.* have studied the structure and bonding of these complexes. The usual composition is  $\text{MX}_2\text{L}_2$  where M is a metal, X a halogen and L a 1,2-dithiole-3-thione. The cobalt(II) complex has a high-spin pseudo-tetrahedral structure.<sup>91</sup> Nickel(II) forms pseudo-tetrahedral as well as square-planar complexes depending on the nature of the substituents in the 1,2-dithiole nucleus.<sup>92</sup> Iron forms normal complexes.<sup>93</sup> If, however, iron(III) is used in a preparation, it is reduced to an iron(II) complex. Likewise copper(II) is reduced to copper(I), giving either  $\text{CuXL}_2$  or  $\text{CuXL}_3$ . The  $\text{CuXL}_2$  complex has dimeric structure **58**. Iron(II) complexes have a pseudo-tetrahedral structure.<sup>93</sup>



(58)

The dimeric mercury(II) complex  $\text{HgX}_2\text{L}$  used for purification of 1,2-dithiole-3-thiones, has been ascribed a distorted tetrahedral symmetry based on infrared studies.<sup>94</sup> The monomeric zinc(II) complex  $\text{ZnX}_2\text{L}_2$  has the

<sup>90</sup> K. Hartke and R. Hoffmann, *Justus Liebigs Ann. Chem.*, 483 (1980).

<sup>91</sup> F. Petillon and J. E. Guerschais, *Bull. Soc. Chim. Fr.*, 2455 (1971).

<sup>92</sup> F. Y. Petillon and J. E. Guerschais, *Can. J. Chem.*, **49**, 2598 (1971).

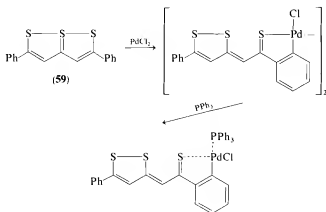
<sup>93</sup> F. Petillon, J. E. Guerschais, and D. M. L. Goodgame, *J. C. S. Dalton*, 1209 (1973).

<sup>94</sup> F. Petillon and J. E. Guerschais, *Int. J. Sulfur Chem.*, **8**, 367 (1973).

same symmetry, whereas tin(IV) forms a trans-octahedral complex  $\text{SnX}_4\text{L}_2$ . Furthermore, complexes of titanium(IV), antimony(V) and (III), and bismuth(III) have been studied.<sup>95</sup> The structure of these complexes is discussed on the basis of their Mössbauer spectra. Zirconium(IV), aluminum(III), magnesium(II), and manganese(II) did not give rise to complexes. In all cases the site of coordination is the thione sulfur. No X-ray structures have been published.

The stability constants of Ag(I) complexes with a series of 1,2-dithiole-3-thiones have been measured in order to obtain quantitative data concerning the complexing ability of the thiones.<sup>96</sup> In most cases kinetic measurements involving rates of methylation provide a better method.<sup>97</sup> 1,2-Dithiole-3-thiones have been used as analytical reagents for metals without further studies of the structure of the complexes formed (cf. Section V).

1,6,6a $\lambda^4$ -Trithiapentalenes (**59**) have been transformed into palladium complexes of the valence tautomeric 1,2-dithiol-3-ylidene thiones, which are vinylogs of 1,2-dithiole-3-thiones<sup>98</sup> (Scheme 5).



SCHEME 5

## B. SALT FORMATION

1,2-Dithiolylum salts are key starting materials for a variety of 1,2-dithiole derivatives. The use of 1,2-dithiolylum salts prepared by standard methods

<sup>95</sup> F. Petillon and J. E. Guerschais, *J. Inorg. Nucl. Chem.* **37**, 1863 (1975).

<sup>96</sup> C. Madec, A. Laouenan, and J. Courtot-Coupez, *J. Chem. Res., Synop.*, 230 (1979).

<sup>97</sup> M. Arbelot, R. Gallo, M. Chanon, and J. Metzger, *Phosphorus Sulfur* **1**, 271 (1976).

<sup>98</sup> B. Bogdanovic, C. Krüger, and P. Locatelli, *Angew. Chem.* **91**, 745 (1979).



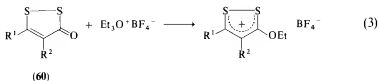
from 1,2-dithiole-3-thiones will not be discussed in this survey (see, for example, Refs. 99 and 100).

Two fundamentally different series of 1,2-dithiolylum salts can be derived from 1,2-dithiole-3-thiones. In one series the thione sulfur is conserved in the salt; in the other series it is substituted by halogen or hydrogen.

The synthesis of 1,2-dithiolylum salts by oxidation of 1,2-dithiole-3-thiones by peracetic acid was originally introduced by Klingsberg.<sup>101,102</sup> Preferred oxidizing agents are peracids or hydrogen peroxide in acetic acid.<sup>103</sup> 1,2-Dithiole-3-thiones bearing bulky substituents can also be oxidized by means of nitric acid<sup>104</sup>; if bulky substituents are not present, the thione or the salt is usually decomposed. The peracid oxidation gives the best result with aromatic substituted 1,2-dithiole-3-thiones, but may also be used with aliphatic or unsubstituted compounds.<sup>105</sup> For details concerning the mechanism of oxidation see Section III.E.

The oxidation with  $D_2O_2$  instead of  $H_2O_2$  gives rise to deuterium-labeled salts.<sup>106,107</sup>

The first type of 1,2-dithiolylum salts described was 3-methylthio-1,2-dithiolylum salts such as **9**,<sup>108</sup> prepared by methylation of the thione group. 3-Arylthio-1,2-dithiolylum salts cannot be prepared by direct arylation of the thione, but have to be prepared either by reaction of 3-halogeno-1,2-dithiolylum salts with silver salts of thiophenols<sup>109</sup> or by photochemical arylation (cf. Section III.G).



<sup>99</sup> H. Prinzbach and E. Futterer, *Adv. Heterocycl. Chem.* **7**, 39 (1966).

<sup>100</sup> N. Lozac'h and M. Stavaux, *Adv. Heterocycl. Chem.* **27**, 151 (1980).

<sup>101</sup> E. Klingsberg, *Chem. Ind. (London)*, 1568 (1960).

<sup>102</sup> E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961).

<sup>103</sup> U.S. Patent 3,791,789 [CA **81**, 155582 (1974)]. Febr. 12, 1974.

<sup>104</sup> U.S. Patent 3,959,313 [CA **85**, 94346 (1976)]. May 25, 1976.

<sup>105</sup> J.-C. Poite, A. Perichaut, and J. Roggero, *C. R. Hebd. Seances Acad. Sci., Ser. C* **270**, 1677 (1970).

<sup>106</sup> R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *Tetrahedron* **22**, 2119 (1966).

<sup>107</sup> G. Duguay and H. Quiniou, *C. R. Hebd. Seances Acad. Sci., Ser. C* **283**, 495 (1976).

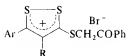
<sup>108</sup> B. Böttcher and A. Lüttringhaus, *Justus Liebigs Ann. Chem.* **557**, 89 (1947).

<sup>109</sup> J. Faust, H. Spies, and R. Mayer, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **22B**, 789 (1967).

It is necessary to use strong alkylating agents such as Merwein salts to alkylate 1,2-dithiol-3-ones (**60**)<sup>110</sup> (Eq. 3). A series of 3-ethoxy-1,2-dithiolylium fluoroborates was prepared and their visible spectra compared to data calculated by means of the SCF-PPP method.<sup>110</sup>

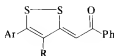
1,2-Dithiole-3-thiones react with  $\alpha$ -bromoketones<sup>111,112</sup> to give crystalline, stable salts (**61**). A few examples have been given by Brown *et al.*<sup>113</sup>

Salts **61** are useful starting materials for the synthesis of 1,2-dithiole-3-ylidene ketones<sup>114,115</sup> (e.g., **61**  $\rightarrow$  **62**). If the dithiole nucleus is substituted in the 4-position, the yield of 1,2-dithiol-3-ylidene ketone is high. But if no substituent is present, as in **61b**, the yield is only 0–15%; disulfide **63** is the main product.

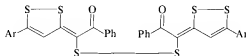


(61a) R = Ar

(61b) R = H



(62)



(63)

3-Acetylthio-1,2-dithiolylium salts have been described.<sup>116</sup> A variety of methods are available for the preparation of 3-halides. The reaction of oxalyl chloride with 1,2-dithiol-3-ones gives 3-chloro-1,2-dithiolylium salts (**66**)<sup>116</sup> (Scheme 6). In some cases the reaction can be realized with 1,2-dithiole-3-thiones too. Phosgene can be used instead of oxalyl chloride. Oxalyl bromide gives the corresponding 3-bromo-1,2-dithiolylium salts.<sup>117</sup> 3-Chloro-1,2-dithiolylium dichlorophosphates have been prepared from 1,2-dithiol-3-ones and phosphorus oxychloride.<sup>118</sup> The corresponding

<sup>110</sup> J. Faust and J. Fabian, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **B24**, 577 (1969).

<sup>111</sup> G. Caillaud and Y. Mollier, *Bull. Soc. Chim. Fr.*, 2018 (1970).

<sup>112</sup> G. Caillaud and Y. Mollier, *Bull. Soc. Chim. Fr.*, 147 (1972).

<sup>113</sup> E. I. G. Brown, D. Leaver, and D. M. McKinnon, *J. Chem. Soc. C*, 1202 (1970).

<sup>114</sup> G. Caillaud and Y. Mollier, *Bull. Soc. Chim. Fr.*, 331 (1971).

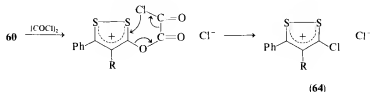
<sup>115</sup> G. Caillaud and Y. Mollier, *Bull. Soc. Chim. Fr.*, 151 (1972).

<sup>116</sup> J. Faust and R. Mayer, *Justus Liebigs Ann. Chem.* **688**, 150 (1965).

<sup>117</sup> J. Faust, H. Spies, and R. Mayer, *Naturwissenschaften* **20**, 537 (1967).

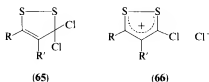
<sup>118</sup> G. A. Reynolds, *J. Org. Chem.* **33**, 3352 (1968).

bromo compounds may be prepared from phosphorus oxybromide.<sup>119</sup> The chloro dithiolium salts have further been prepared from 1,2-dithiole-3-thiones and trichloromethyl isocyanodichloride or thiophosgene; these reagents have the advantage that the thione can be used directly.<sup>120</sup>



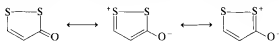
SCHEME 6

Chlorinated products obtained from 1,2-dithiole-3-thiones and chlorine have been ascribed dichloride structure **65**, but have been shown to be isomeric salts **66**.<sup>116</sup>



### C. REACTIONS WITH GRIGNARD REAGENTS

The reaction of 1,2-dithiol-3-ones with Grignard reagents has been studied in detail by Boberg and co-workers. Owing to resonance structures such as



SCHEME 7

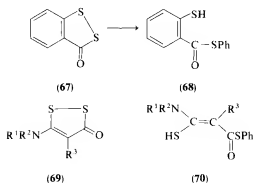
those shown in Scheme 7, nucleophilic attack on the sulfur atoms can occur with subsequent ring opening. Thus 1,2-benzodithiolone (**67**) gives *o*-mercaptothiolobenzoic acid esters (**68**)<sup>121</sup> when treated with a Grignard reagent. With phenylmagnesium bromide 5-amino-4-aryl-1,2-dithiol-3-ones (**69**) give thioamides (**70**).<sup>121, 121a</sup>

<sup>119</sup> C. T. Pedersen and N. Lozac'h, *Acta Chem. Scand.* **24**, 3189 (1970).

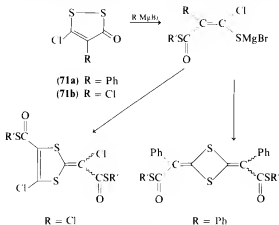
<sup>120</sup> F. Boberg and W. von Gentzkow, *Justus Liebigs Ann. Chem.* **766**, 1 (1972).

<sup>121</sup> F. Boberg and R. Schardt, *Justus Liebigs Ann. Chem.* **728**, 44 (1969).

<sup>121a</sup> F. Boberg and R. Schardt, *Justus Liebigs Ann. Chem.* **734**, 173 (1970).



5-Chloro-1,2-dithiol-3-ones (e.g., **71a**) and 4,5-dichloro-1,2-dithiol-3-one (**71b**) react with Grignard reagents on sulfur with subsequent ring closure of the open-chain intermediates.<sup>121b</sup> The dithiethanes were isolated in 57–97% yields. Both *cis* and *trans* isomers were formed. Dichloro compound **71b** gives via thioketene derivatives 1,3-dithiol-2-ylidene compounds in 12–75% yield. Mixtures of stereoisomers were obtained<sup>121b</sup> (Scheme 8).



SCHEME 8

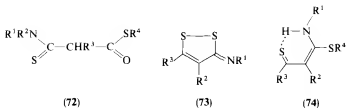
5-Amino-4-aryl-1,2-dithiol-3-ones (**69**) and 5-(*N*-aryl-*N*-alkylamino)-4-chloro-1,2-dithiol-3-ones give rise to derivatives of thiomalonic acid (**72**) in the reaction with Grignard reagents.<sup>121c</sup> 3-Imino-1,2-dithioles (**73**) react in an analogous manner and give open chain thionoamides (**74**).<sup>121c,121d,122</sup>

<sup>121b</sup> F. Boberg, M. Ghoudikian, and M. H. Khorgami, *Justus Liebigs Ann. Chem.*, 1261 (1974).

<sup>121c</sup> F. Boberg, J. Schröder, and R. Schardt, *Justus Liebigs Ann. Chem.*, 2260 (1976).

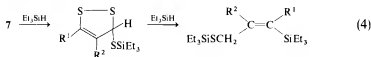
<sup>121d</sup> F. Boberg and W. von Gentzkow, *Justus Liebigs Ann. Chem.*, 247 (1973).

<sup>122</sup> F. Boberg and W. von Gentzkow, *J. Prakt. Chem.*, 315, 970 (1973).

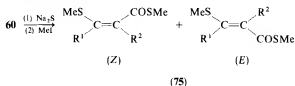


## D. REDUCTIONS

The reduction of 1,2-dithiole-3-thiones (7) by means of triethylsilane probably involves an addition of the silane to the thiocarbonyl group with subsequent opening of the ring and reaction with one further mole of triethylsilane<sup>123</sup> (Eq. 4).



1,2-Dithiole-3-thiones and 1,2-dithiol-3-ones can be reduced by sodium sulfide with opening of the ring. The methylated products were isolated.<sup>124</sup> The products (75) from the reduction of 1,2-dithiol-3-ones **60** were isolated in both *Z* and *E* forms, whereas only the *Z* form could be isolated in the reduction of 1,2-dithiole-3-thiones (7) although both forms were present in solution, probably due to the equilibrium  $Z \rightleftharpoons E$ . In all cases the yields of isolated products were 45–95%.



SCHEME 9

Electrochemical reduction of 1,2-dithiole-3-thiones on a platinum electrode gives rise to the same products (see Section III.H).

The reduction product obtained from 1,2-benzodithiolethione (**23**) has been ascribed different structures.<sup>125,126</sup> The structure of the compound

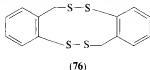
<sup>123</sup> F. Blazy, J. Bonastre, and G. Pfister-Guillouzo, *Bull. Soc. Chim. Fr.*, 4247 (1968).

<sup>124</sup> J. Maignan and J. Vialle, *Bull. Soc. Chim. Fr.*, 1973 (1973).

<sup>125</sup> A. Mannesier, *Gazz. Chim. Ital.* **46**, 231 (1916).

<sup>126</sup> A. Lüttringhaus and K. Hagele, *Angew. Chem.* **67**, 304 (1955).

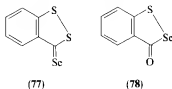
obtained by reduction with  $\text{LiAlH}_4$  is dibenzo[*c,h*]-2*H*,10*H*-dihydro-1,2,8,9-tetrathiecine (76) as indicated by EI-, FD-, and CI-mass spectrometry.<sup>127</sup>



### E. OXIDATION

The oxidation of 1,2-dithiole-3-thiones by peracetic acid has long been used for the preparation of 1,2-dithiolylum salts.<sup>128</sup> The reaction actually involves a reduction of the heterocyclic system, the exocyclic sulfur atom being oxidized to sulfate ion. The oxidation of 1,2-dithiole-3-thiones by peracids has been studied in connection with a systematic study of the oxidation of heterocyclic thiones.<sup>129</sup> The general conclusion is that salt formation is the normal reaction, if the ring system does not bear strong electron-withdrawing substituents and is not fused with an aromatic ring. In other cases 1,2-dithiol-3-ones are formed, or, as in the case of benzo-condensed compounds, poorly defined oxidation products are formed.<sup>130</sup> Surprisingly, 3*H*-naphtho[1,2-*c*]-1,2-dithiole-3-thione gives a 1,2-dithiolylum salt in 38% yield.<sup>130</sup>

The oxidation reaction is probably complex, as shown by the oxidation of 4,5-benzo-3-selenoxo-1,2-dithiole (77) with benzoyl peroxide.<sup>131</sup> This oxidation does not give rise to 1,2-benzodithiolone but 4,5-benzo-1,2-thiaselenol-3-one (78). The results from oxidation with  $^{18}\text{O}$ -labeled benzoyl



peroxide are in agreement with the formation of a selenine intermediate (Scheme 10). The presence of such intermediates is consistent with results

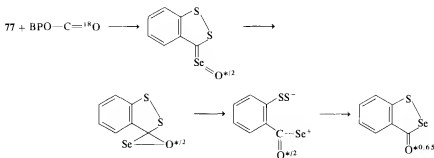
<sup>127</sup> R. T. Parfitt, D. E. Games, R. F. Cookson, A. C. Richards, and N. Lynaugh, *Org. Mass Spectrom.* **13**, 341 (1978).

<sup>128</sup> E. Klingsberg, *Chem. Ind. (London)*, 1568 (1960).

<sup>129</sup> J. L. Charlton, S. M. Loosmore, and D. M. McKinnon, *Can. J. Chem.* **52**, 3021 (1974).

<sup>130</sup> E. Klingsberg, *J. Org. Chem.* **37**, 3226 (1972).

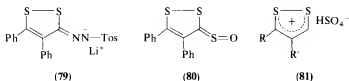
<sup>131</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Heterocycles* **2**, 45 (1974).



SCHEME 10

obtained by sulfuration of 1,2-dithiol-3-ones with <sup>35</sup>S-labeled phosphorus pentasulfide.<sup>132</sup> The oxidation of 1,2-benzodithiolethione by means of tetrachloro-*o*-quinone gives 1,2-benzodithiolone via a 1,2-benzodioxole derivative.<sup>133</sup>

Sulfines **80** were obtained from the thermolysis of lithium salts of tosylhydrazones of 1,2-dithiol-3-ones (**79**) in the presence of oxygen.<sup>134</sup> A series of these *S*-oxides was obtained by oxidation of 1,2-dithiole-3-thiones with one equivalent of peracid under conditions where the *S*-oxide precipitates. Further addition of peracid gave the 1,2-dithiolylum salt (**81**).<sup>134</sup> The sulfines can be prepared from *m*-chloroperbenzoic acid in 30–70% yields and with sodium periodate as an oxidant.<sup>135</sup> Oxidation with reactive reagents such as (PhO)<sub>3</sub>PO<sub>3</sub>, O<sub>3</sub>, NaOCl, benzoyl peroxide, and HgO gave 1,2-dithiol-3-one via the sulfine.<sup>135</sup>



Oxidation of 1,2-benzodithiolethione with singlet oxygen gives 1,2-benzodithiolone via the sulfine, which could be isolated.<sup>136</sup> The *S*-monoxide (**82a**) and the *S,S*-dioxide (**82b**) were isolated from the oxidation of 1,2-benzodithiolone with *m*-perchlorobenzoic acid.<sup>137</sup> The formation of *S*-oxides

<sup>132</sup> U. Schmidt, *Justus Liebig's Ann. Chem.* **635**, 109 (1960).

<sup>133</sup> N. Latif, A. Nada, H. M. El-Namaky, and B. Haggag, *Indian J. Chem., Sect. B* **18B**, 131 (1979).

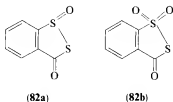
<sup>134</sup> E. Meinetsberger, Ph.D. Thesis, University of Munich (1978).

<sup>135</sup> S. Tamagaki, K. Hotta, and S. Kozuka, *Chem. Lett.*, 619 (1980).

<sup>136</sup> S. Tamagaki and K. Hotta, *J. C. S. Chem. Commun.*, 598 (1980).

<sup>137</sup> A. G. Hortmann, A. J. Aron, and A. K. Bhattacharya, *J. Org. Chem.* **43**, 3374 (1978).

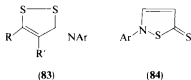
has been claimed in patents without structural proof.<sup>138</sup> Electrochemical oxidation of 1,2-dithiole-3-thiones on a platinum electrode gives rise to disulfide-linked oxidation products (see Section III,H).



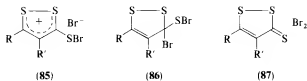
## F. RING TRANSFORMATION

The transformation of the 1,2-dithiole ring into other heterocycles is described in other sections, e.g., formation of the 1,3-dithiole system by addition of alkenes in Section III,J; by addition of alkynes in Section III,G; and formation of the 1,6,6aλ<sup>4</sup>-trithiapentalene in Section III,I.

The products from the reaction of aryl amines with the 1,2-dithiole-3-thione-Br<sub>2</sub> complex have been described both as imines (83)<sup>139,140</sup> and as isothiazolin-5-thiones (84).<sup>141,142</sup>



Possible structures of the addition product derived from 1,2-dithiole-3-thiones and bromine are 85, 86 and 87.



<sup>138</sup> U.S. Patent 3,376,225 [CA 68, 106655 (1968)] Apr. 2, 1968.

<sup>139</sup> J. P. Biton, G. Duguay, and H. Quiniou, *C. R. Hebd. Seances Acad. Sci., Ser. C* **267**, 586 (1968).

<sup>140</sup> J. L. Adelfang, *J. Org. Chem.* **31**, 2388 (1966).

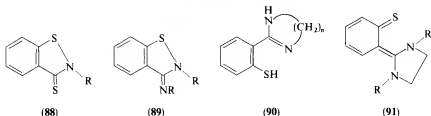
<sup>141</sup> G. E. Bachers, D. M. McKinnon, and J. M. Buchschrer, *Can. J. Chem.* **50**, 2568 (1972).

<sup>142</sup> F. Boberg and W. von Gentzkow, *J. Prakt. Chem.* **315**, 965 (1973).

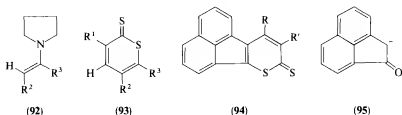


1,2-Benzodithiolethione, gives both isothiazole (88) and the imine (89)<sup>143,144</sup> with amine nucleophiles.

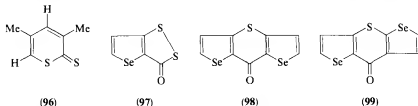
1,2-Benzodithiolethione with diamines gives cyclic amidines (90) in which two sulfur atoms are lost.<sup>145</sup> The reaction of *N,N'*-dialkyl-1,2-diaminoethanes with 1,2-benzodithiolethione gives products 91<sup>146</sup> which are nitrogen analogs of those obtained from alkenes (see Section III.G).



Enamines (92) with 1,2-dithiole-3-thiones unsubstituted in the 5-position give thiopyrane-2-thiones (93).<sup>147,148</sup> Formation of thiopyrane-2-thiones (94) from enolate ion 95 has been described.<sup>149</sup>



The reaction of alkali metal salts of  $\alpha,\beta$ -ethylene thiolates with 4-methyl-1,2-dithiole-3-thiones produces thiopyrane-2-thiones 96.<sup>150</sup> Reaction of



<sup>143</sup> H. Böshagen, H. Feltkamp, and W. Geiger, *Chem. Ber.* **100**, 2435 (1967).

<sup>144</sup> A. Baruffini, P. Borgna, and L. Amoretti, *Farmaco* **23**, 574 (1968).

<sup>145</sup> J. P. Brown, *J. C. S. Perkin I*, 869 (1974).

<sup>146</sup> R. Okazaki, K.-T. Kang, and N. Inamoto, *Heterocycles* **9**, 1741 (1978).

<sup>147</sup> F. Ishii, M. Stavaux, and N. Lozac'h, *Tetrahedron Lett.*, 1473 (1975).

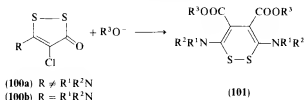
<sup>148</sup> F. Ishii, M. Stavaux, and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1142 (1977).

<sup>149</sup> N. K. Son, R. Pincel, and Y. Mollier, *Bull. Soc. Chim. Fr.*, 3334 (1973).

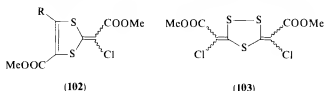
<sup>150</sup> N. A. Bunina, M. L. Petrov, and A. A. Petrov, *Zh. Org. Khim.* **15**, 2306 (1979).

3H-selenolo[2,3-*d*]-1,2-dithiol-3-one (**97**) with copper gives the two isomeric thiopyrones **98** and **99**.<sup>150a</sup>

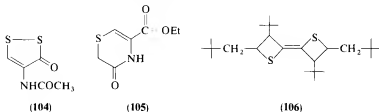
1,2-Dithiacyclohexadienes (**101**) can be obtained from the alcoholysis of 4-chloro-5-amino-1,2-dithiol-3-ones (**100a**).<sup>151</sup>



4-Chloro-1,2-dithiol-3-ones (**100a**) give with sodium alkoxides 1,3-dithiole derivatives **102**, together with 1,2,4-trithiacyclopentanes (**103**).<sup>152,153</sup>



In connection with studies of the 1,2-dithiole antibiotics thiolutin and holomycin it was observed that 4-acetamido-1,2-dithiol-3-one (**104**) is converted to thiazine **105** by sodium ethanolate.<sup>154</sup> Compound **106** allegedly forms from 5-(*tert*-butyl)-4-neopentyl-1,2-dithiole-3-thione and trimethyl phosphite,<sup>155</sup> but no proof was given for the structure.



The alkaline hydrolysis of 1,2-dithiol-3-ones is complex; the reaction products<sup>155a</sup> include the two sulfur-containing systems **107** and **108**.

<sup>150a</sup> K. Beelitz and K. Praefcke, *Justus Liebigs Ann. Chem.*, 1620 (1980).

<sup>151</sup> F. Boberg, H. Niemann, and K. Kirchoff, *Justus Liebigs Ann. Chem.* **728**, 32 (1969).

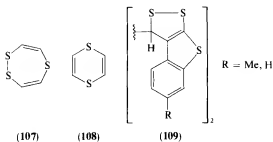
<sup>152</sup> J. Bader, *Helv. Chim. Acta* **51**, 1421 (1968).

<sup>153</sup> F. Boberg and M. Ghoudikian, *Justus Liebigs Ann. Chem.*, 1513 (1975).

<sup>154</sup> R. F. C. Brown and I. D. Rae, *Aust. J. Chem.* **18**, 1071 (1965).

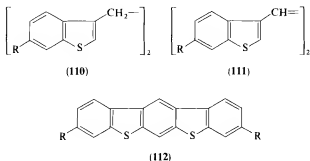
<sup>155</sup> U.S. Patent 3,427,246 [*CA* **70**, 79768 (1969)]. Febr. 11, 1969.

<sup>155a</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **683**, 132 (1965).



## G. PHOTOCHEMISTRY

De Mayo and co-workers have studied the photochemistry of 1,2-dithiole-3-thiones in connection with general studies of the photochemistry of thioketones.<sup>156</sup> 5-Aryl-substituted compounds were photochemically stable, whereas 4-aryl-substituted isomers gave "dimers" **109** as the main product. Minor amounts of compounds not containing the 1,2-dithiole nucleus **110**, **111**, and **112** were isolated.<sup>156</sup>

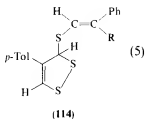
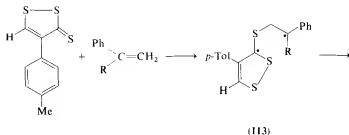


Irradiation of 4-*p*-tolyl-1,2-dithiole-3-thione in the presence of styrene or  $\alpha$ -methylstyrene gave products (**114**) formed by addition to the thiocarbonyl group<sup>156</sup> (Eq. 5). The diradical **113** was proposed as an intermediate. This reaction is different from the one described by Okazaki *et al.*<sup>157,158</sup> for 5-phenyl-1,2-dithiole-3-thione (**2**) and 4,5-diphenyl-1,2-dithiole-3-thione (**7**),

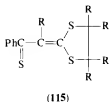
<sup>156</sup> P. de Mayo and H. Y. Ng, *Tetrahedron Lett.*, 1561 (1973).

<sup>157</sup> R. Okazaki, F. Ishii, K. Ozawa, and N. Inamoto, *Chem. Lett.*, 9 (1972).

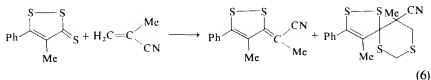
<sup>158</sup> R. Okazaki, F. Ishii, K. Ozawa, K. Ozawa, and N. Inamoto, *J. C. S. Perkin I*, 270 (1975).



with an alkene where the formation of 1,3-dithioles (115) is suggested. This reaction is proposed to proceed via the same biradical proposed by de Mayo.



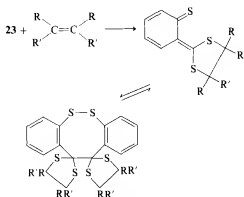
Photolysis of 4-methyl-5-phenyl-1,2-dithiole-3-thione in the presence of methacrylonitrile gives a mixture of two products<sup>159</sup> (Eq. 6).



The photolysis of 1,2-benzodithiolethione in the presence of cyclic and acyclic alkenes gives blue *o*-methylenethioquinone systems in high yields.

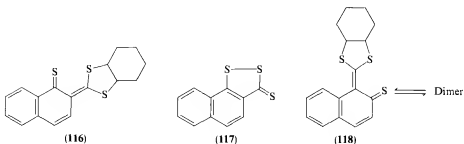
<sup>159</sup> V. N. Drozd, G. S. Bogomolova, and Y. M. Udachin, *Zh. Obshch. Khim.* **14**, 2459 (1978).

The blue compounds are in equilibrium with colorless eight-membered dimers<sup>160-164</sup> (Scheme 10).



SCHEME 10

A stable *o*-thioquinomethide (**116**) has been isolated from naphtho[2,1-*d*]-1,2-dithiole-3-thione **117** and cyclohexene in the crystalline state. The product **118** derived from the isomeric naphtho[1,2-*d*]-1,2-dithiole-3-thione could not be isolated in the pure state, but only as an adduct with *N*-phenylmaleimide.<sup>165</sup>



The photolysis of 4-methyl-5-phenyl-1,2-dithiole-3-thione (**119**) in the presence of alkynes gives a mixture of 1,3-dithiole derivatives and a

<sup>160</sup> P. de Mayo and H. Y. Ng, *J. C. S. Chem. Commun.*, 877 (1974).

<sup>161</sup> P. de Mayo and H. Y. Ng, *Can. J. Chem.*, **55**, 3763 (1977).

<sup>162</sup> R. Okazaki and N. Inamoto, *Chem. Lett.*, 1439 (1974).

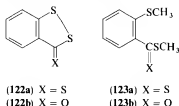
<sup>163</sup> R. Okazaki, F. Ishii, K. Sunagawa, and N. Inamoto, *Chem. Lett.*, 51 (1978).

<sup>164</sup> R. Okazaki, K. Sunagawa, K.-T. Kang, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **52**, 496 (1979).

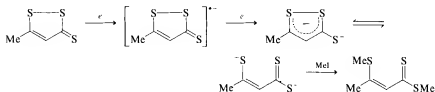
<sup>165</sup> R. Okazaki, K. Sunagawa, M. Kotera, and N. Inamoto, *Tetrahedron Lett.*, 3815 (1976).



sulfate.<sup>170</sup> In most cases methylated reduction products **123a** and **123b** could be isolated in preparative electrolysis.

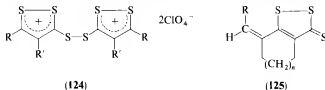


The preparative reduction, polarography, and cyclic voltammetry of 5-methyl-1,2-dithiole-3-thione have been studied.<sup>171</sup> The results obtained are in agreement with a one-electron reduction of the thiocarbonyl group to a radical-anion, which could not be detected by ESR spectroscopy as it dimerizes too fast. The dimer is further reduced by a one-electron reduction to an anion in which the ring has been opened. (Scheme 12). The dianion could be isolated after methylation and was found to be identical with the compounds isolated by Maignan and Vialle by reduction with sodium sulfide.<sup>124</sup> The dianion corresponds to the thioketonate dianion obtained by electrochemical reduction of 1,2-dithiolium salts.<sup>172</sup>



SCHEME 12

The anodic oxidation of a series of substituted 1,2-dithiole-3-thiones has been studied and S—S linked dications **124** were isolated. Oxidation and



<sup>170</sup> D. Kunz, H. Hartmann, and R. Mayer, *Z. Chem.* **9**, 60 (1969).

<sup>171</sup> A. Astruc, M. Astruc, D. Conbeau, and G. Pfister-Gouillouzo, *Collect. Czech. Chem. Commun.* **39**, 861 (1974).

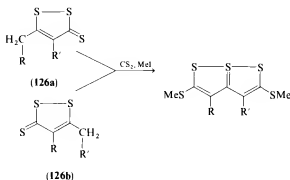
<sup>172</sup> K. Bechgaard, V. P. Parker, and C. T. Pedersen, *J. Am. Chem. Soc.* **95**, 4373 (1973).

reduction potentials were given.<sup>173</sup> Cyclic voltammetric data are reported for 3-ethylthio-1,2-dithiolylum hexafluorophosphate.<sup>173a</sup>

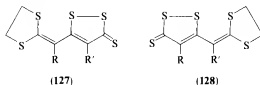
### I. REACTIONS INVOLVING THE SIDE CHAIN

5-Methyl or methylene groups in 1,2-dithiole-3-thiones condense readily with aromatic aldehydes with formation of 5-styryl-1,2-dithiole-3-thiones **125**.<sup>174</sup>

Carbon disulfide has been condensed with 1,2-dithiole-3-thiones having a methylene group in the 5-position.<sup>175</sup> In no case could the initially formed condensation product be isolated. In all cases the two isomeric 1,2-dithiole-3-thiones **126a** and **126b** gave the same 1,6,6a $\lambda^4$ -trithiapentalene.



However, with 1,2-dibromoethane as alkylating agent, the reaction of **126a** and **126b** gave two isomeric alkylated products **127** and **128**.<sup>176</sup> Carbon oxydisulfide has been found to react in the presence of methyl iodide to yield two methylated products<sup>177,178</sup> (Scheme 13).



<sup>173</sup> C. T. Pedersen and V. D. Parker, *Tetrahedron Lett.*, 771 (1972).

<sup>173a</sup> R. D. Braun and D. C. Green, *J. Electroanal. Chem.* **79**, 381 (1977).

<sup>174</sup> H. Hartmann and R. Mayer, *Z. Chem.* **5**, 151 (1965).

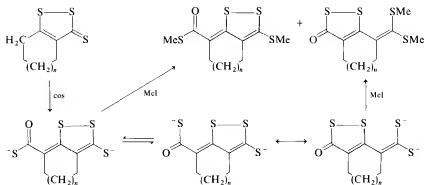
<sup>175</sup> C. Portail and J. Vialle, *Bull. Soc. Chim. Fr.*, 3187 (1966).

<sup>176</sup> J.-L. Burgot and J. Vialle, *Bull. Soc. Chim. Fr.*, 137 (1974).

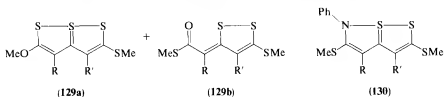
<sup>177</sup> J.-L. Burgot and J. Vialle, *Bull. Soc. Chim. Fr.*, 3333 (1969).

<sup>178</sup> J.-L. Burgot, *Bull. Soc. Chim. Fr.*, 140 (1974).



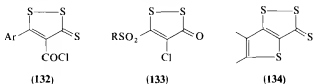


Burgot and Vialle found that *O*-methyl dithiocarbonate condenses in an analogous manner<sup>179</sup> with **126a** to form isomers **129a** and **129b**.



Diethyl acetals of *N,N*-dimethylaminoformaldehyde react with 5-methyl-1,2-dithiole-3-thione<sup>180</sup> giving enamine **8** ( $R = H$ ). Analogous condensation products could be obtained from thioformyl amines. Condensation of phenyl isothiocyanate with **126a** gave 6-aza-1,6aλ<sup>4</sup>-dithiapentalenes (**130**),<sup>181</sup> after methylation.

4-Carboxy-1,2-dithiole-3-thiones can be converted to acid chlorides **132** by means of thionyl chloride.<sup>182</sup> In the usual way these chlorides form esters and amides, and they can take part in Friedel-Crafts reactions. 5-Aryl-Substituted 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones react with



<sup>179</sup> J.-L. Burgot and J. Vialle, *C. R. Hebd. Seances Acad. Sci., Ser. C* **278**, 793 (1974).

<sup>180</sup> C. Metayer, G. Duguay, and H. Quiniou, *Bull. Soc. Chim. Fr.*, 163 (1974).

<sup>181</sup> J.-L. Burgot and J. Vialle, *Bull. Soc. Chim. Fr.*, 1499 (1976).

<sup>182</sup> C. Trebaul, *Bull. Soc. Chim. Fr.*, 1840 (1972).

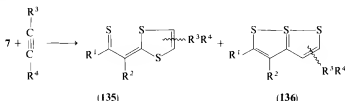
chlorosulfonic acid in the aromatic nucleus.<sup>183</sup> 1,2-Dithiol-3-ones with alkylthio substituents can be oxidized to sulfones (133).<sup>184,185</sup>

5-Vinyl-1,2-dithiole-3-thiones react with sulfur to form thieno[3,2-*c*]-1,2-dithiole-3-thiones (134).<sup>186-188</sup> 4-Amino-1,2-dithiole-3-thiones can be N-alkylated and N-acylated.<sup>189</sup>

## J. REACTIONS INVOLVING THE C=S BOND

Photochemical addition to the C=S bond has been treated in Section III.G.

The thermal addition of alkynes to the C=S bond has been studied independently by groups headed by Behringer<sup>190,191</sup> McKinnon,<sup>192-194</sup> Vialle,<sup>195-198</sup> and Leaver.<sup>199,200</sup> All have observed that the reaction between 1,2-dithiole-3-thiones (7) and activated acetylenes such as aryl substituted alkynes and acetylene mono- and dicarboxylic acid esters gives rise to a mixture of 2-thioacylmethylene-1,3-dithioles (135) and 1,6,6aλ<sup>4</sup>-trithiapentalenes (136).



<sup>183</sup> A. Dorange and F. Venien, *C. R. Hebd. Seances Acad. Sci., Ser. C* **279**, 237 (1974).

<sup>184</sup> Swiss Patent 447,207 [*CA* **69**, 59216 (1968)] Mar. 29, 1968.

<sup>185</sup> British Patent 1,103,128 [*CA* **69**, 36105 (1968)] Febr. 14, 1968.

<sup>186</sup> J. Brelivet, P. Appriou, and J. Teste, *C. R. Hebd. Seances Acad. Sci., Ser. C* **265**, 1010 (1967).

<sup>187</sup> P. Appriou, J. Brelivet, and J. Teste, *Bull. Soc. Chim. Fr.*, 1497 (1970).

<sup>188</sup> J. Brelivet, P. Appriou, and J. Teste, *Bull. Soc. Chim. Fr.*, 1344 (1971).

<sup>189</sup> R. F. C. Brown, I. D. Rae, and S. Sternhell, *Aust. J. Chem.*, **18**, 61 (1965).

<sup>190</sup> H. Behringer and R. Wiedenmann, *Tetrahedron Lett.*, 3705 (1965).

<sup>191</sup> H. Behringer, D. Bender, J. Falkenberg, and R. Wiedenmann, *Chem. Ber.* **101**, 1428 (1968).

<sup>192</sup> J. M. Buchshriber, D. M. McKinnon, and M. Ahmed, *Can. J. Chem.* **47**, 2039 (1969).

<sup>193</sup> M. Ahmed, J. M. Buchshriber, and D. M. McKinnon, *Can. J. Chem.* **48**, 1991 (1970).

<sup>194</sup> D. M. McKinnon and J. M. Buchshriber, *Can. J. Chem.* **49**, 3299 (1971).

<sup>195</sup> H. Davy, M. Demuyne, D. Paquer, A. Rouessac, and J. Vialle, *Bull. Soc. Chim. Fr.*, 1150 (1966).

<sup>196</sup> H. Davy, M. Demuyne, D. Paquer, A. Rouessac, and J. Vialle, *Bull. Soc. Chim. Fr.*, 2057 (1968).

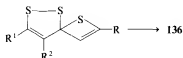
<sup>197</sup> H. Davy and J. Vialle, *Bull. Soc. Chim. Fr.*, 1435 (1975).

<sup>198</sup> H. Davy and J.-M. Decrouen, *Bull. Soc. Chim. Fr.*, 115 (1976).

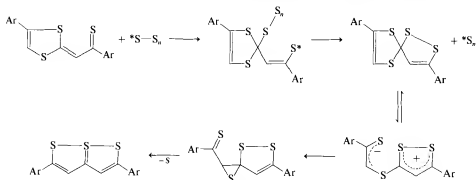
<sup>199</sup> D. B. J. Easton and D. Leaver, *J. C. S. Chem. Commun.*, 585 (1965).

<sup>200</sup> D. B. J. Easton, D. Leaver, and T. J. Rawlings, *J. C. S. Perkin I*, 41 (1972).

No systematic studies of the reaction mechanism have been undertaken, but it is suggested that the 1,3-dithiole derivative is formed directly by a 1,3-dipolar cycloaddition where the thiocarbonyl serves as the negative end of the dipole. The formation of 1,6,6a $\lambda^4$ -trithiapentalenes may start with a 1,2-addition of the alkyne to the thiocarbonyl group, followed by a rearrangement to give **136**.

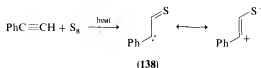


However, 1,3-dithioles can be rearranged to 1,6,6a $\lambda^4$ -trithiapentalenes, catalyzed by various sulfur-containing compounds, such as 1,2-dithiole-3-thiones,<sup>201</sup> thioacetamide,<sup>202</sup> phosphorus pentasulfide, elemental sulfur, dibenzylthiocarbamate, 2-mercaptobenzothiazole and tetramethyl thiuramdisulfide.<sup>203</sup> (Scheme 14). This mechanism, however, cannot account for the



SCHEME 14

total amount of 1,6,6a $\lambda^4$ -trithiapentalene formed; another mechanism must also be operative. It is suggested that the trithiapentalene is formed by a direct addition of sulfur to the alkyne via a thioacyl carbene **138**.<sup>203</sup> Alkyl-substituted 1,2-dithiole-3-thiones give 1,6,6a $\lambda^4$ -trithiapentalenes much more readily than aryl-substituted counterparts.



<sup>201</sup> J. Vialle, *Q. Rep. Sulfur Chem.*, **5**, 151 (1970).

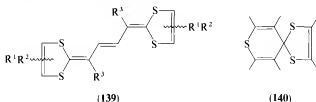
<sup>202</sup> H. Davy and J. Vialle, *C. R. Hebd. Seances Acad. Sci.*, **275**, 625 (1972).

<sup>203</sup> S. Davidson and D. Leaver, *J. C. S. Chem. Commun.*, 540 (1972).

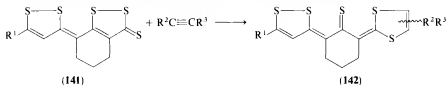
The most convenient synthesis of the parent 1,6,6a $\lambda^4$ -trithiapentalene is the isomerization of the addition product from 1,2-dithiole-3-thione and methyl propiolate.<sup>202</sup>

Thioaldehydes have rarely been described in literature. If an alkyne is added to 5-unsubstituted 1,2-dithiole-3-thiones, ethylenic thioaldehydes (e.g., **135**, R<sup>1</sup> = H) can be isolated. They are described by McKinnon as amorphous, unstable compounds,<sup>194</sup> but Davy has isolated them as crystalline, stable compounds<sup>197</sup> with well-defined mass spectra.<sup>204</sup>

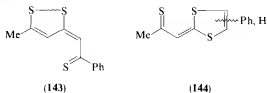
Prolonged heating of the addition compounds may result in the loss of sulfur, whereby "dimeric" products **139** are formed.<sup>197</sup> Addition of one further mole of alkyne to the 2-thioacylmethylene-1,3-dithiole gives rise to spiranic thiopyrane derivatives **140**.<sup>192</sup>



The addition of alkynes has also been carried out with extended 1,2-dithiole-3-thiones (**141**).<sup>205</sup> Adducts (**142**) from this reaction could not be isomerized to compounds with five sulfur atoms in a row.



A compound formed by the reaction of thioacetic acid with phenylacetylene in the presence of sodium acetate and described as *trans*-trithiapentalene (**143**)<sup>206</sup> has been shown to be the isomeric 1,3-dithiol-2-ylidenepropanethione (**144**) formed initially from 5-methyl-1,2-dithiole-3-thione and phenylacetylene.<sup>207</sup>



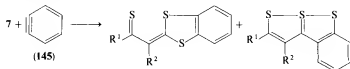
<sup>204</sup> C. T. Pedersen, H. Davy, J. Møller, and J. Vialle, *Acta Chem. Scand., Ser. B* **B28**, 964 (1974).

<sup>205</sup> M. Stauvaux, *Bull. Soc. Chim. Fr.*, 4426 (1971).

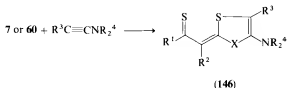
<sup>206</sup> H. Behringer, *Chemia* **19**, 132 (1965).

<sup>207</sup> C. T. Pedersen, *Acta Chem. Scand., Ser. B* **B28**, 367 (1974).

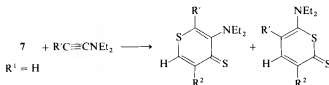
Benzyne (**145**) also reacts with 1,2-dithiole-3-thiones (**7**).<sup>208,209</sup> The 1,6,6aλ<sup>4</sup>-trithiapentalene seems not to be formed by isomerization of the 1,3-dithiole derivative in this case.



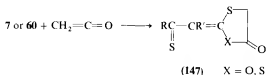
1,2-Dithiole-3-thiones (**7**) and 1,2-dithiol-3-ones (**60**), which do not possess a proton in the 5-position, react with ynamines in the same way as simple alkynes do, to give **146**; moreover, the reaction is also possible with 1,2-dithiol-3-ones.<sup>210</sup>



If a proton is present in the 5-position of **7** ( $R^1 = H$ ), the reaction product is a mixture of a thiopyrane-2-thione and a thiopyrane-4-thione.



Ketene itself reacts with 1,2-dithiole-3-thiones with formation of a 1,3-dithiolane derivative.<sup>211,212</sup> In the same manner a 1,2-dithiol-3-one gives a 1,3-oxathiolane derivative (**147**).



<sup>208</sup> J.-M. Decrouen, D. Paquer, and R. Pou, *C. R. Hebd. Seances Acad. Sci., Ser. C* **279**, 259 (1974).

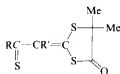
<sup>209</sup> D. Paquer and R. Pou, *Bull. Soc. Chim. Fr.*, 120 (1976).

<sup>210</sup> A. Dibo, M. Stauvaux, and N. Lozac'h, *Bull. Soc. Chim. Fr.* **2**, 530 (1980).

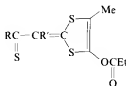
<sup>211</sup> G. Hervieu, P. Rioult, and J. Vialle, *Bull. Soc. Chim. Fr.*, 4375 (1971).

<sup>212</sup> G. Hervieu, P. Rioult, and J. Vialle, *Bull. Soc. Chim. Fr.*, 4380 (1971).

Dimethylketene reacts in the same way and gives **148**, whereas methylene gives the enolester (**149**).<sup>212</sup> The reaction of diphenylketene with 1,2-dithiole-3-thiones occurs with loss of the thiocarbonyl sulfur<sup>213</sup> (e.g., **150**). It is suggested that this reaction proceeds via the normal 1,3-dithiolane derivative.<sup>211</sup>



(148)

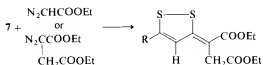


(149)



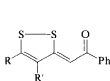
(150)

The reaction of various diazo compounds with 1,2-dithiole-3-thiones has been studied<sup>214</sup> (Scheme 15). If the 1,2-dithiole-3-thione is unsubstituted in the 4-position, the reaction product from diazoacetic ester is the same succinate as that formed from diazosuccinate.



SCHEME 15

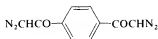
Diazoketones give rise to 1,2-dithiol-3-ylidene ketones (**151**). The reaction has also been carried out with more complex diazoketones such as **152** and **153**, which give analogous products.



(151)



(152)



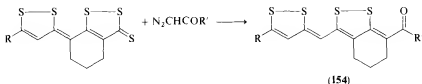
(153)

The reaction with diazoketones has been used for the preparation of intermediates **154** in the synthesis of compounds with a row of five sulfur atoms.<sup>215</sup>

<sup>213</sup> P. Rioult and J. Vialle, *Bull. Soc. Chim. Fr.*, 2883 (1967).

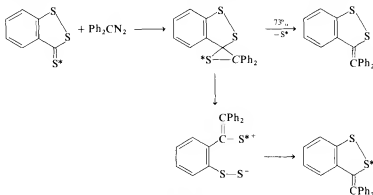
<sup>214</sup> Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 2090 (1967).

<sup>215</sup> M. Stavaux, *Bull. Soc. Chim. Fr.*, 4429 (1971).



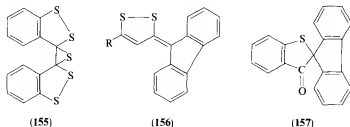
The reaction of diphenyldiazomethane with 1,2-dithiole-3-thiones gave the same compounds **150** as those isolated from the reaction with diphenylketene.<sup>214</sup>

It has been claimed that 1,2-benzodithiolethione did not react with diphenyldiazomethane<sup>216</sup>; this has been shown to be incorrect.<sup>217,218</sup> By use of <sup>35</sup>S two possible pathways for the reaction were found (Scheme 16).



SCHEME 16

The reaction of 1,2-benzodithiolethione with diazomethane gave the thiirane (**155**).<sup>219</sup> With 1,2-dithiole-3-thiones diazofluorene gave normal products **156**, whereas 1,2-benzodithiolethione gave the spiro compound **157**.



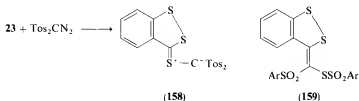
<sup>216</sup> A. Schönberg and R. von Ardenne, *Chem. Ber.* **101**, 346 (1968).

<sup>217</sup> S. Tamagaki, R. Ichihara, and S. Oae, *Bull. Chem. Soc. Jpn.* **48**, 355 (1975).

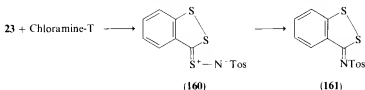
<sup>218</sup> S. Tamagaki and R. Ichihara, *Heterocycles* **4**, 963 (1976).

<sup>219</sup> M. A.-F. Elkashef, F. M. E. Abdel-Megeid, and A. A. Elbarbary, *Acta Chim. Acad. Sci. Hung.* **93**, 157 (1977).

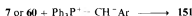
Bis(*p*-toluenesulfonyl)diazomethane has been reported to give ylids **158** with 1,2-dithiole-3-thiones.<sup>220</sup> However, the alternative structure **159** has also been suggested.<sup>218</sup>



The reaction of 1,2-dithiole-3-thiones with chloramine-T results in formation of analogous nitrogen compounds (e.g., **160**), which may lose the exocyclic sulfur atom to form **161**.<sup>220</sup> Other *N*-chloramines have been used.<sup>221,222</sup> The chemistry of these imines has been studied.<sup>223-230</sup>



The reaction of phosphorus ylids gives rise to 1,2-dithiol-3-ylidene ketones **151**.<sup>231</sup>



1,2,3-Dithiazines, urethanes, or iminocarboxylic acid esters result from the reaction of ethyl azidoformate with 1,2-dithiole-3-thiones.<sup>232</sup>

Tetracyanoethylene oxide reacts with 1,2-dithiole-3-thiones with formation of 1,2-dithiol-3-ylidene malonitriles **162**; these could also be obtained from tetracyanoethylene.<sup>233</sup>

<sup>220</sup> S. Tamagaki and S. Oae, *Tetrahedron Lett.*, 1159 (1972).

<sup>221</sup> F. Boberg, G.-J. Wentrup, and M. Koepke, *Synthesis*, 502 (1975).

<sup>222</sup> G.-J. Wentrup and F. Boberg, *Justus Liebigs Ann. Chem.*, 387 (1978).

<sup>223</sup> S. Tamagaki and S. Oae, *Bull. Chem. Soc. Jpn.* **46**, 2608 (1973).

<sup>224</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Heterocycles* **2**, 39 (1974).

<sup>225</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Tetrahedron Lett.*, 1059 (1974).

<sup>226</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Jpn.* **47**, 3084 (1974).

<sup>227</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Heterocycles* **2**, 631 (1974).

<sup>228</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Jpn.* **48**, 2983 (1975).

<sup>229</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Jpn.* **48**, 2985 (1975).

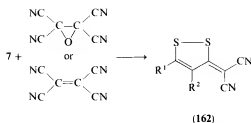
<sup>230</sup> S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Jpn.* **48**, 2987 (1975).

<sup>231</sup> R. S. Tewari and K. C. Gupta, *Synth. Commun.* **8**, 315 (1978).

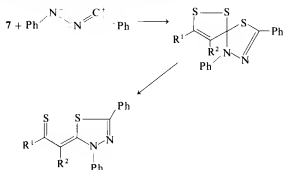
<sup>232</sup> M. S. Chauhan and D. M. McKinnon, *Can. J. Chem.* **54**, 3879 (1976).

<sup>233</sup> A. Rouessac and J. Vialle, *Bull. Soc. Chim. Fr.*, 2054 (1968).



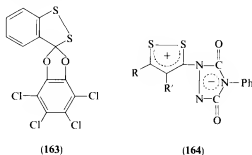


1,2-Dithiole-3-thiones with  $\alpha$ -chlorobenzylidene phenylhydrazine undergo 1,3-dipolar cycloaddition<sup>234,235</sup> (Scheme 17).



SCHEME 17

With tetrachloro-*o*-benzoquinone 1,2-benzodithiolethione gives a spirane (163).<sup>236</sup> 4-Phenyl-1,2,4-triazoline-3,5-dione forms mesoionic compounds (e.g., 164) with 1,2-dithiole-3-thiones.<sup>237,238</sup>



<sup>234</sup> Y. Poirier, *Bull. Soc. Chim. Fr.*, 1203 (1968).

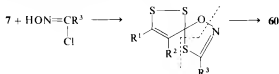
<sup>235</sup> M. Maguet, Y. Poirier, and J. Teste, *Bull. Soc. Chim. Fr.*, 1503 (1970).

<sup>236</sup> N. Latif, A. Nada, H. El-Namaky, and B. Haggag, *Chem. Ind. (London)*, 706 (1975).

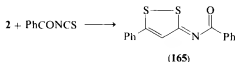
<sup>237</sup> V. N. Drozd and G. S. Bogomolova, *Zh. Org. Khim.* **13**, 2012 (1977).

<sup>238</sup> V. N. Drozd, V. M. Fedoseev, G. S. Bogomolova, V. V. Sergeichuk, N. M. Semenenko, and A. A. Mandrugun, *Zh. Org. Khim.* **16**, 198 (1980).

1,2-Dithiole-3-thiones can be converted to 1,2-dithiol-3-ones by means of hydroxamic acid chlorides<sup>239</sup> (e.g., **7** → **60**).



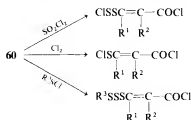
Oximes have been formed from 1,2-dithiole-3-thiones and hydroxylamine.<sup>240</sup> 1,2-Dithiole-3-thiones react with acyl isothiocyanates to give **165**.<sup>241</sup>



### K. FORMATION OF OPEN-CHAIN COMPOUNDS

Examples of formation of open-chain compounds may also be found in Section III.C.

When 1,2-dithiol-3-ones react with sulfuryl chloride, chlorine,<sup>242</sup> or sulfonyl chlorides,<sup>243</sup> the compounds shown in Scheme 18 are obtained.



SCHEME 18

Desulfurization of 1,2-dithiole-3-thiones with trivalent phosphorus compounds has been studied.<sup>244</sup> Monophenyl-substituted compounds are

<sup>239</sup> F. Boberg and J. Knoop, *Justus Liebigs Ann. Chem.* **708**, 148 (1967).

<sup>240</sup> H. Böshagen and W. Geiger, *Justus Liebigs Ann. Chem.*, 20 (1977).

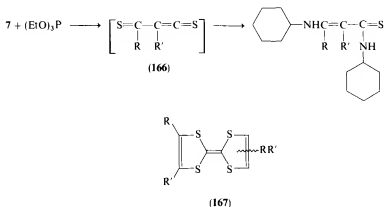
<sup>241</sup> A. Grandin and J. Vialle, *Bull. Soc. Chim. Fr.*, 1851 (1967).

<sup>242</sup> T. P. Vasil'eva, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Iz. Akad. Nauk SSSR, Ser. Khim.*, 643 (1974).

<sup>243</sup> T. P. Vasil'eva, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Iz. Akad. Nauk SSSR, Ser. Khim.*, 2610 (1975).

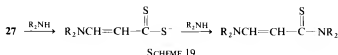
<sup>244</sup> J. Goerdeler, J. Haug, C. Lindner, and R. Losch, *Chem. Ber.* **107**, 502 (1974).

unaffected by triphenylphosphine, whereas 4,5-diphenyl and 4-phenyl-5-cyano-1,2-dithiole-3-thione are desulfurized. If the desulfurization is carried out in cyclohexylamine, the enamino derivative is isolated; this is indicative of the formation of a thioacyl thioketene (**166**) intermediate. 1,2-Dithiole-3-thiones behave differently from the analogous 1,3-dithiole-2-thiones, which give 1,1',3,3'-tetrathiafulvalenes (**167**) with trivalent phosphorus compounds.<sup>245</sup>



Various open-chain compounds have been isolated from the alkaline hydrolysis of 1,2-dithiole-3-thiones.<sup>246</sup>

The parent 1,2-dithiole-3-thione reacts with amines under mild conditions (e.g., 100° C)<sup>247</sup> (Scheme 19).



## L. MISCELLANEOUS

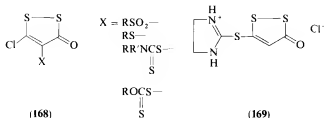
The 5-chloro substituent in 5-chloro-1,2-dithiole-3-ones (**168**) can be replaced by a large number of sulfur-containing nucleophiles.<sup>248</sup> With *N,N'*-ethylenethiourea the isothiuronium salt **169** is isolated.

<sup>245</sup> M. Marita and C. V. Pittman, Jr., *Synthesis*, 489 (1976).

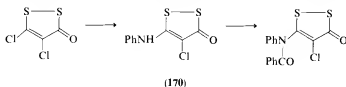
<sup>246</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **683**, 132 (1965).

<sup>247</sup> E. J. Smutny, W. Turner, E. D. Morgan, and R. Robinson, *Tetrahedron* **23**, 3785 (1967).

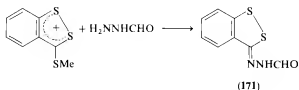
<sup>248</sup> J. Bader, *Helv. Chim. Acta* **51**, 1409 (1968).



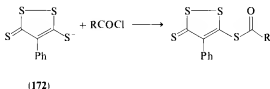
4,5-Dichloro-1,2-dithiol-3-one reacts with aromatic amines<sup>249</sup> giving **170**. The 5-phenylamino group in 1,2-dithiol-3-ones may be benzoylated.<sup>250</sup>



A 3-methylthio group reacts with hydrazines to form hydrazones **171**, which cannot be obtained directly from the thiones and hydrazines.<sup>251</sup>



The thiolate group in 4-phenyl-3-thioxo-1,2-dithiole-5-thiolate (**172**) can be acylated.<sup>252</sup>



The desulfurization of 1,2-dithiole-3-thione with copper bronze has given the results shown in Scheme 20.<sup>253</sup>

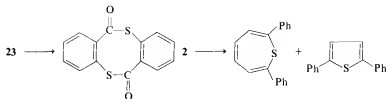
<sup>249</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **681**, 169 (1965).

<sup>250</sup> S. Hünig, G. Kiesslich, K.-H. Oette, and H. Quast, *Justus Liebigs Ann. Chem.* **754**, 46 (1971).

<sup>251</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **681**, 178 (1965).

<sup>252</sup> N. Loyaza and C. T. Pedersen, *Acta Chem. Scand., Ser. B* **B30**, 88 (1976).

<sup>253</sup> M. A.-F. Elkashef, F. M. E. Abdel-Megeid, and A. A. Elbarbary, *Tetrahedron* **30**, 4113 (1974).



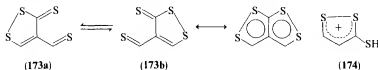
SCHEME 20

## IV. Physical Properties

### A. THEORETICAL STUDIES

Together with theoretical studies of other sulfur systems calculations have been made on 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones.<sup>254,255</sup>

In a study of various thiocarbonyl systems the equilibrium  $173a \rightleftharpoons 173b$  has been discussed. It was concluded that the energy difference between a structure of  $C_{2v}$  and  $C_s$  symmetry is  $\sim 35$  kcal/mol.<sup>256</sup>



The electronic transitions for the parent 1,2-dithiole-3-thione have been calculated using a PPP-SCF method without explicit inclusion of sulfur d-orbitals.<sup>257</sup> Good agreement with observed values was found. Other calculations also have been reported.<sup>258</sup>

A modified CNDO method has been used for the calculation of the electronic spectra of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones<sup>259,260</sup>; good agreement with observed data was found. The method has further been used to interpret the modification of the electronic spectrum of 1,2-dithiole-3-thione by protonation in sulfuric acid between 1 and 20 N,<sup>261</sup> forming the 3-mercapto-1,2-dithiolylium ion 174. On the basis of acidity functions it has

<sup>254</sup> J. Fabian, A. Melhorn, J. Bormann, and R. Mayer, *Wiss. Z. Tech. Univ., Dresden* **14**, 285 (1965).

<sup>255</sup> R. Mayer, H. Hartmann, J. Fabian, and A. Melhorn, *Z. Chem.* **7**, 209 (1967).

<sup>256</sup> G. Calzaferri and R. Gleiter, *J. C. S. Perkin II*, 559 (1975).

<sup>257</sup> R. A. W. Johnstone and S. D. Ward, *Tetrahedron* **25**, 5485 (1969).

<sup>258</sup> J. Fabian, *Z. Chem.* **13**, 26 (1973).

<sup>259</sup> G. Pfister-Guillouzo, D. Gonbeau, and J. Deschamps, *Bull. Soc. Chim. Belg.* **80**, 311 (1971).

<sup>260</sup> G. Pfister-Guillouzo, D. Gonbeau, and J. Deschamps, *J. Mol. Struct.* **14**, 95 (1972).

<sup>261</sup> D. Gonbeau, C. Guimon, and G. Pfister-Guillouzo, *Tetrahedron* **29**, 3599 (1973).

been concluded that various 1,2-dithiole-3-thiones are protonated on the thiocarbonyl sulfur in strong acid.<sup>262</sup>

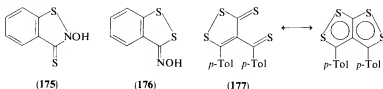
A simple LCAO-MO calculation suggests that the heterocyclic ring in phenyl-substituted 1,2-dithiole-3-thiones has aromatic character; however, the S—S bond is almost excluded from conjugation.<sup>263</sup> It was found that the phenyl group in 4-phenyl-1,2-dithiole-3-thione had the character of an electron acceptor, whereas that of 5-phenyl-1,2-dithiole-3-thione had electron-donating properties.

The heats of formation for three 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones indicate that the 1,2-dithiole system possesses a delocalized  $\pi$ -electron sextet.<sup>264</sup>

The addition of alkynes to 1,2-dithiole-3-thiones has been studied by means of CNDO/2 methods.<sup>265</sup>

## B. STRUCTURE DETERMINATION

Space group and unit cell dimensions are given for 4,5-diphenyl-1,2-dithiole-3-thione.<sup>266</sup> The reaction product from 1,2-benzodithiolethione and hydroxylamine was originally ascribed the isothiazole structure **175**.<sup>267</sup> However, X-ray structure studies have shown it to be 1,2-benzodithiolone oxime. (**176**).<sup>268</sup>



The sulfocarbon **37** has been ascribed the thione structure<sup>72</sup>; X-ray structure determination has shown that it corresponds better with a trithiapentalene-like structure **38**, a thia analog of coronene.<sup>73</sup>

No-bond-single-bond resonance should be possible in **177** according to theoretical studies,<sup>256</sup> but X-ray analysis did not substantiate this.<sup>269</sup>

<sup>262</sup> J. T. Edward, I. Lantos, G. D. Derdall, and S. G. Wong, *Can. J. Chem.* **55**, 812 (1977).

<sup>263</sup> M. G. Voronkov, V. I. Minkin, O. A. Osipov, M. G. Kogan, and T. V. Lapina, *Khim. Geterosikl. Soedin.* **3**, 758 (1967).

<sup>264</sup> G. Geiseler and H.-J. Rauh, *Z. Phys. Chem. (Leipzig)* **249**, 376 (1972).

<sup>265</sup> R. Pinel, M. Gelize-Duvigneau, M. Z. Benabdallah, and J. Arriau, *Bull. Soc. Chim. Belg.* **89**, 187 (1980).

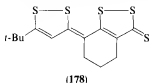
<sup>266</sup> A. Hordvik, E. Sletten, and J. Sletten, *Acta Chem. Scand.* **20**, 1171 (1966).

<sup>267</sup> E. W. McClelland and C. E. Salkeld, *J. Chem. Soc.*, 1143 (1936).

<sup>268</sup> G. D. Andreotti, L. Cavalca, A. Manfredotti, and A. Musatti, *Acta Crystallogr., Sect. B* **B25**, 288 (1969).

<sup>269</sup> P.-T. Cheng and S. C. Nyburg, *J. C. S. Perkin II*, 1854 (1977).

The structure of extended 1,2-dithiole-3-thiones **178** has been studied<sup>270</sup> and the structure of the 1,2-dithiole-3-thione part of the molecule was found to be much like that of 4-methyl-1,2-dithiole-3-thione.<sup>271</sup>



### C. INFRARED SPECTROSCOPY

The infrared spectra of a series of 1,2-dithiole-3-thiones have been studied and five types of IR bands were located and assigned.<sup>272</sup> Electron delocalization in 1,2-dithiol-3-ones of the type shown in Scheme 7 was discussed on the basis of IR frequencies of the carbonyl absorption and dipole moments.<sup>273</sup> These parameters suggest that ionic structures contribute rather strongly to the structure of 1,2-dithiol-3-ones.

IR and Raman spectra of a series of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones have been recorded and interpreted.<sup>274</sup> Sixteen of the eighteen fundamental ring vibrations of the parent 1,2-dithiole-3-thione have been observed, and most of the substituent frequencies have been assigned.

### D. ESCA AND PHOTOELECTRON SPECTRA

In connection with other 1,2-dithiole derivatives the ESCA spectra of 1,2-dithiole-3-thiones and 5-phenyl-1,2-dithiol-3-one have been discussed.<sup>275</sup> In the thiones it was found that thiocarbonyl sulfur had an average binding energy near that of dithiocarboxylate sulfur. This means that a positive charge is present in the ring, i.e., mesoionic forms such as **179** must contribute considerably to the structure. The same is true for the 1,2-dithiol-3-one.



<sup>270</sup> J. Sletten, *Acta Chem. Scand.* **26**, 873 (1972).

<sup>271</sup> G. A. Jeffrey and R. Shiono, *Acta Crystallogr.* **12**, 447 (1959).

<sup>272</sup> J. Fabian and R. Mayer, *Chem. Ind. (London)*, 1962 (1966).

<sup>273</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **693**, 212 (1966).

<sup>274</sup> D. Gentric and P. Saumagne, *Int. J. Sulfur Chem., Part A* **2**, 15 (1972).

<sup>275</sup> B. J. Lindberg, S. Högberg, G. Malmsten, J.-E. Bergmark, Ö. Nilsson, S.-E. Karlsson, A. Fahlman, U. Gelus, R. Pinel, M. Stavaux, Y. Mollier, and N. Lozac'h, *Chem. Ser.* **1**, 183 (1971).

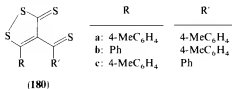
The He(I) photoelectron spectra of a series of 1,2-dithiole-3-thiones have been studied.<sup>276</sup> The ionization energies of  $\pi$  and  $n$  electrons of the C=S group as well as those of the perturbed  $\pi$  electrons of the disulfide group were measured. In this way information concerning the interaction between the 1,2-dithiole ring and the thiocarbonyl group was obtained. The observations were compared to data obtained by CNDO/s calculations.

### E. NUCLEAR MAGNETIC RESONANCE SPECTRA

From <sup>1</sup>H-NMR spectra of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones it was not possible to draw conclusions concerning the pseudoaromatic character of the 1,2-dithiole-3-thione system.<sup>277</sup> Proton chemical shifts of methyl substituents are in agreement with values reported for methyl substituents in aromatic systems.<sup>278</sup> Calculated diamagnetic and paramagnetic anisotropies for a series of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones have been compared with observed chemical shifts. Analysis of these data suggests that a phenyl substituent in position 5 is nearly coplanar with the dithiole nucleus and that the 1,2-dithiole nucleus is an electron-attracting group.<sup>279</sup>

Lanthanide induced chemical shifts have been studied.<sup>280</sup> 1,2-Dithiole-3-thiones did not give any contact shifts with Eu(fod)<sub>3</sub> and Pr(fod)<sub>3</sub>, whereas 1,2-dithiol-3-ones gave moderate shifts. Attempts to define the position of lanthanide complexing were made for the 1,2-dithiol-3-ones; it was not possible to define the position of the lanthanide atom closer than 2–3 Å from the oxygen and 40–50° on either side of the C—O line.

The valence tautomerism in compounds **180** has been discussed on the basis of <sup>1</sup>H-NMR data. Although no-bond resonance did not render the tolyl groups in **180a** equivalent (two methyl signals were observed), two different compounds could not be isolated in attempts to prepare potential isomers **180b** and **180c**. The same was found for acyl compounds.<sup>281</sup>



<sup>276</sup> D. Gonbeau, C. Guimon, J. Dechamps, and G. Pfister-Guillouzo, *J. Electron Spectrosc. Relat. Phenom.* **6**, 99 (1975).

<sup>277</sup> R. F. C. Brown, I. D. Rae, and S. Sternhell, *Aust. J. Chem.* **18**, 1211 (1965).

<sup>278</sup> P. S. Landis, *J. Chem. Eng. Data* **11**, 412 (1966).

<sup>279</sup> A. Dorange, F. Tonnard, and F. Venien, *C. R. Hebd. Seances Acad. Sci., Ser. C* **276**, 1057 (1973).

<sup>280</sup> I. D. Rae, *Aust. J. Chem.* **28**, 2527 (1975).

<sup>281</sup> E. I. G. Brown, D. Leaver, and T. J. Rawlings, *J. C. S. Chem. Commun.*, 83 (1969).



$^{13}\text{C}$  chemical shifts are shown in Table I. The chemical shift of C-3 is nearly unaffected by substitution, whereas some influence on those for C-4 and C-5 is observed. The  $\alpha$ -substituent effect for phenyl substituents in the thione series produced by a 5-phenyl group is approximately twice that produced by a 4-phenyl group.<sup>282</sup>

TABLE I  
 $^{13}\text{C}$  CHEMICAL SHIFTS OF 1,2-DITHIOLE-3-THIONES (7) AND 1,2-DITHIOL-3-ONES (60)

R <sup>1</sup>	R <sup>2</sup>	3-X	C-3	C-4	C-5	Reference
H	H	S	216.7	140.2	155.1	282 <sup>a</sup>
Me	H	S	216.7	139.4	172.1	283 <sup>a</sup>
<i>i</i> -Bu	H	S	215.96	136.25	187.86	284 <sup>a</sup>
Me	Me	S	214.54	142.01	165.59	284
Me	<i>i</i> -Pr	S	215.6	149.5	168.1	283
—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	H	S	215.3	143.4	169.2	283
Ph	H	S	215.8	136.2	172.9	282, 283
			215.45	135.54	173.54	285 <sup>b</sup>
4-MeC <sub>6</sub> H <sub>4</sub>	H	S	215.0	135.1	173.0	283
4-FC <sub>6</sub> H <sub>4</sub>	H	S	215.7	136.1	171.3	283
4-ClC <sub>6</sub> H <sub>4</sub>	H	S	215.4	136.1	171.1	283
4-BrC <sub>6</sub> H <sub>4</sub>	H	S	215.5	136.2	171.2	283
3-MeOC <sub>6</sub> H <sub>4</sub>	H	S	216.6	136.2	172.8	283
4-MeOC <sub>6</sub> H <sub>4</sub>	H	S	214.8	134.4	173.0	282
H	Ph	S	213.8	149.2	154.1	282
H	4-MeC <sub>6</sub> H <sub>4</sub>	S	213.45	148.82	152.75	284
Ph	Ph	S	214.9	145.7	170.3	282
Me	Ph	S	214.22	147.06	168.11	284
4-MeOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	S	214.28	144.09	169.67	284
Ph	Cl	S	205.99	<sup>c</sup>	164.88	284
Ph	H	O	193.9	117.7	170.2	282
			193.99	117.80	170.10	285
H	Ph	O	193.9	117.7	170.2	282
4-MeOC <sub>6</sub> H <sub>4</sub>	H	O	193.43	134.18	164.47	284
Ph	Ph	O	193.4	131.6	166.8	282

<sup>a</sup> In CDCl<sub>3</sub>.

<sup>b</sup> In DMSO-*d*<sub>6</sub>.

<sup>c</sup> Obscured by phenyl group.

A correlation has been established between  $^{19}\text{F}$  chemical shifts and the  $S\ 2p$  electron energies obtained from ESCA spectra in a series of fluorine-

<sup>282</sup> N. Plavac, I. W. J. Still, M. S. Chauhan, and D. M. McKinnon, *Can. J. Chem.* **53**, 836 (1975).

<sup>283</sup> B. S. Pedersen and S.-O. Lawesson, *Tetrahedron* **35**, 2433 (1979).

<sup>284</sup> C. T. Pedersen, unpublished results.

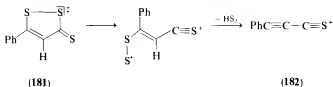
<sup>285</sup> E. G. Frandsen and J. P. Jacobsen, *Org. Magn. Reson.* **10**, 43 (1977).

substituted 1,2-dithiole compounds including 5-(*p*-fluorophenyl)-1,2-dithiole-3-thione and the corresponding oxygen compound.<sup>286</sup>

### F. MASS SPECTROMETRY

Mass spectral data are given as structural proofs in connection with synthesis of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones, but few systematic studies have been published.

The mass spectra of a series of methyl and phenyl substituted compounds have been studied.<sup>287</sup> A general feature of these mass spectra is that the base peak is normally due to the molecular ion. 5-Monosubstituted compounds (e.g., **181**) show intense peaks corresponding to  $M - HS_2$  (**182**), which can be formed by the fragmentation shown, such ions are also found in the mass spectra of  $\alpha$ -(1,3-dithiole-3-ylidene)thioketones and have been used in the discussion of the structure of these compounds.<sup>204</sup>



The mass spectra of 1,2-dithiole-3-thiones bearing functional groups such as  $-\text{NH}_2$ ,  $-\text{CONH}_2$ ,  $-\text{COOC}_2\text{H}_5$ , and  $-\text{CN}$  have been reported<sup>288</sup> along with spectra of extended 1,2-dithiole-3-thiones **178**.<sup>289</sup> These compounds do not show peaks corresponding to  $M - HS_2$  as observed for simple 1,2-dithiole-3-thiones. Prominent peaks due to loss of  $S_2$  and  $HS$  are observed.

### G. CONDUCTIVITY

1,2-Dithiole-3-thiones and 1,2-dithiol-3-ones form adducts with each other which are isolable.<sup>290</sup>

The conductivity of mixed solutions of thiones and corresponding oxygen compounds has been measured; conductivities in the order of  $10^{-14}$  ohm<sup>-1</sup>

<sup>286</sup> B. J. Lindberg, R. Pinel, and Y. Mollier, *Tetrahedron* **30**, 2537 (1974).

<sup>287</sup> C. T. Pedersen and J. Møller, *Acta Chem. Scand.* **26**, 250 (1972).

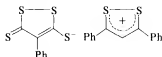
<sup>288</sup> M. Yokoyama, *Bull. Chem. Soc. Jpn.* **43**, 2938 (1970).

<sup>289</sup> C. T. Pedersen, M. Stavaux, and J. Møller, *Acta Chem. Scand.* **26**, 3875 (1972).

<sup>290</sup> F. Boberg, *Justus Liebigs Ann. Chem.* **681**, 169 (1965).

were observed; this was found to be in accordance with a charge transfer via a solvent molecule.<sup>291</sup>

The conductivity of a series of 1,2-dithiole-3-thiones has been measured both in solution and in the solid state. Conductivities were found to be in the range of  $10^{-14}$ – $10^{-15}$  ohm<sup>-1</sup> reflecting an electronic tunneling effect. Dipole moments were given too.<sup>292</sup>



(183)

The 5-thioxo-1,2-dithiole-3-thiolate anion forms charge-transfer complexes with 1,2-dithiolylium ions.<sup>293,294</sup> The structure of the complex **183** has been reported. The low conductivity ( $10^{-12}$  ohm<sup>-1</sup>) was explained by donor and acceptor molecules existing in mixed stacks. The conductivity of a series of analogous complexes was found to be much lower.

## V. Uses

1,2-Dithiole-3-thiones are known for their choloretic activity; most used is 5-(*p*-methoxyphenyl)-1,2-dithiole-3-thione (trithioanethole).<sup>89</sup> Trithioanethole has been used for treatment of salivary insufficiency (dryness of the mouth).<sup>295–298</sup> 1,2-Dithiole-3-thiones and 1,2-dithiol-3-ones have been used against various fungi.<sup>25,70,299–303</sup> 1,2-Dithiole-3-thiones have a remarkable effect on *Schistosoma mansoni* (bilharziosis).<sup>57,59</sup> 1,2-Dithiole-3-thiones and

<sup>291</sup> H. F. Eicke and J. Knoop, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **23B**, 165 (1968).

<sup>292</sup> H. F. Eicke, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **24B**, 210 (1969).

<sup>293</sup> N. Loayza and C. T. Pedersen, *J. C. S. Chem. Commun.*, 496 (1975).

<sup>294</sup> O. Simonsen, N. Loayza, and C. T. Pedersen, *Acta Chem. Scand., Ser. B* **B31**, 281 (1977).

<sup>295</sup> S. R. Bähring-Kuhlmeier, *Med. Actuel.* **14**, 229 (1978).

<sup>296</sup> J. Breunbach and H. Dvorák, *Strahlentherapie* **148**, 298 (1974).

<sup>297</sup> J. Bruck, *Wien. Med. Wochenschr.* **124**, 495 (1974).

<sup>298</sup> R. de Buck, *Acta Psychiatr. Belg.* **73**, 510 (1973).

<sup>299</sup> P. K. Misra, S. C. Misra, R. M. Mohapatra, and A. S. Mitra, *J. Indian Chem. Soc.* **61**, 404 (1979).

<sup>300</sup> J. Ponchet, E. Ventura, G. Berthier, and G. Auge, *Phytiatr.-Phytopharm.* **14**, 133. (1965).

<sup>301</sup> A. J. Latham and M. B. Linn, *Plant Dis. Rep.* **49**, 398 (1965).

<sup>302</sup> L. H. Purdy, *Plant Dis. Rep.* **49**, 42 (1965).

<sup>303</sup> German Patent 1,278,701 [CA **70**, 115147 (1969)]. Sept. 26, 1968.

1,2-dithiol-3-ones have been used as insecticides.<sup>299</sup> Trithioanethole has been used against diseases of the thyroid gland.<sup>304</sup> The diuretic properties of a series of substituted 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones have been studied.<sup>304a</sup> 1,2-Dithiole-3-thiones have been used as additives for lubricating oil.<sup>20,155,305-307</sup> They have been used as vulcanization accelerators<sup>31</sup> and as detergents.<sup>308</sup> Mixtures of 1,2-dithiol-3-ones and *tert*-butyl hydroperoxides have been used for slime control in papermaking.<sup>309</sup> Analytical methods for the determination of the purity of trithioanethole have been given.<sup>310</sup> Spectrophotometric determination of trithioanethole has been carried out in the presence of iron(III) chloride.<sup>311</sup> In connection with a study of the correlation between the structure of thiocarbonyl compounds and their bitter taste, thirty-four 1,2-dithiole-3-thiones have been studied.<sup>312</sup>

<sup>304</sup> L. Jirousek, *Endocrinol. Exp.* **1**, 35 (1962).

<sup>304a</sup> B. Dartiques, J. Cambar, C. Trebaul, J. Brelivet, and R. Guglielmetti, *Eur. J. Med. Chem.* **15**, 405 (1980).

<sup>305</sup> British Patent 1,117,500 [*CA* **69**, 45108 (1968)], Jun. 19, 1968.

<sup>306</sup> Ger. Offen. 2,427,852 [*CA* **83**, 10037 (1975)], Jan. 16, 1975.

<sup>307</sup> Ger. Offen. 2,606,101 [*CA* **87**, 8473 (1977)], Aug. 26, 1976.

<sup>308</sup> U. S. Patent 3,364,232 [*CA* **68**, 60776 (1968)], Jan. 16, 1968.

<sup>309</sup> Canadian Patent 968,707 [*CA* **84**, 95281 (1976)], Jun. 3, 1975.

<sup>310</sup> M. Pochet, S. van Vlasselaer, M. Charon, and M. Denis, *J. Pharm. Belg.* **25**, 263 (1970).

<sup>311</sup> G. Linari and R. Marri, *Boll. Chim. Farm.* **105**, 853 (1966).

<sup>312</sup> R. Mayer and F. Wittig, *Z. Chem.* **12**, 91 (1972).

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## Azocines

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## I. Introduction

### A. SCOPE

This review covers nonannelated and annelated eight-membered heterocycles containing one nitrogen. However, it does not include polycyclic structures where nitrogen is the bridgehead atom (1), nor where nonadjacent ring carbons are linked by a bridge (2).

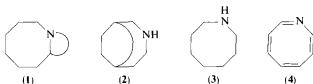
### B. NOMENCLATURE

#### 1. *The Old and New Nomenclature*

Before Volume 41 of *Chemical Abstracts* (1947), the eight-membered monocyclic saturated heterocycle with one nitrogen (3) was referred to as "heptamethyleneimine." From Volume 41 through Volume 55 (1961) of *Chemical Abstracts*, a dual system of naming was used. The old "heptamethyleneimine" term was retained, whereas the Hantzsch-Widman System was introduced.<sup>1</sup> The compound with four noncumulative double bonds was termed "azocine" (4), and saturation was expressed by the detachable prefixes tetrahydro-, hexahydro-, and octahydro-. Under both systems, the nitrogen is designated as atom "1." Beginning with Volume 56 of *Chemical*

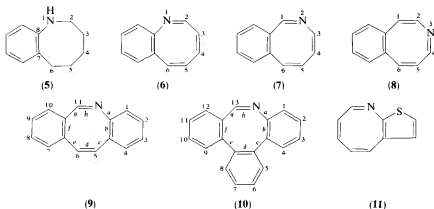
<sup>1</sup> The reader is referred to "Nomenclature of Organic Chemistry," issued by the Commission on Nomenclature of Organic Chemistry, International Union of Pure and Applied Chemistry, 3rd ed., Butterworth, London, 1971, Section B, from which this section was taken. See also "The Naming and Indexing of Chemical Compounds from Chemical Abstracts" (reprint of the Introduction to the Subject Index to Volume 56 (Jan.-June 1962) of *Chemical Abstracts*, Chemical Abstracts Service, American Chemical Society, Easton, Pennsylvania, 1962, ¶¶ 132-146.

*Abstracts.* only the Hantzsch-Widman nomenclature has been used. Occasionally, one encounters names not strictly in accordance with prescribed terminology, e.g., "azocane" or "azacyclooctane" to denote the saturated, eight-membered heterocycle containing one nitrogen. In this article, we are more concerned with clarity, than with the consistent use of IUPAC nomenclature.



## 2. Fused Ring Systems

A bicyclic, fused benzene ring and a heterocyclic eight-membered ring with one nitrogen may be designated as either "benzoheptamethyleneimine" or "benzazocine." Using the former system, the position of the benzene ring with respect to the nitrogen is denoted by two numbers (e.g., **5** is "7,8-benzoheptamethyleneimine"). Using the azocine system, the three possible benzo-fused isomers (**6**, **7**, and **8**) would be named 1-, 2-, and 3-benzazocine, respectively. When the azocine ring is fused with two or more benzene rings, fusion positions are indicated by lettering the sides of the azocine "a," "b," "c," etc., beginning with "a" for side 1,2; "b" for 2,3; etc. For example, **9** is dibenz[*b,f*]azocine and **10** tribenz[*b,d,f*]azocine. The numbering begins with the benzene carbon adjacent to the azocine ring and *not* with an azocinyl carbon as was the case with monobenzazocines. If the azocine contains simple fused carbocyclic rings, naming is as above. For example, a cyclopentane-fused azocine would be cyclopent[*a*]azocine, cyclopent[*b*]azocine,







(12)



(13)



(14)

etc. When heterocyclic rings are fused to the azocine, naming must not only provide for location of fusion on the eight-membered ring, but also for fusion of the azocine on the other ring. For example, **11**, **12**, and **13** would be called thieno[2,3-*b*]azocine, thieno[2,3-*c*]azocine, and thieno[3,2-*b*]azocine, respectively. When the eight-membered ring is part of a spiran, the compound is named as a spiroalkane with the position of the nitrogen denoted by "aza," prefixed with a number. For example, **14** is called 10-azaspiro[5,7]tridecane.

## II. Azocines

### A. PREPARATIVE METHODS

#### 1. Via Ring Closure

Braun and Muller attempted an azocine synthesis in 1906;<sup>2</sup> 7-bromo- or 7-chloroheptylamine with alkali gave some partially crystalline solid whose empirical formula was correct for heptamethyleneimine but whose molecular weight could not be determined. The cyclization of 7-chlorooctylamine gave a product considered to be 2-methylheptamethyleneimine.<sup>3</sup> Tokamoto obtained perhydroazocine (**3**) from 7-bromo-1-aminoheptane and aqueous base,<sup>4</sup> and enantholactam (**15**) by cyclization of the corresponding amino acid.<sup>5</sup> Catecholborane as a catalyst for the reaction affords mostly lactam dimer.<sup>6</sup> Other cyclizations of aminoalkanes having similar leaving groups have been reported.<sup>7-11</sup> The first successful application of the Dieckmann reaction to eight-membered ring closure was Leonard and Stentz's synthesis of 1,2-dimethyl-1-azacyclooctane-3-one.<sup>12</sup> This same approach was used to

<sup>2</sup> J. V. Braun and C. V. Muller, *Ber. Dtsch. Chem. Ges.* **39**, 4110 (1906).

<sup>3</sup> S. Gabriel, *Ber. Dtsch. Chem. Ges.* **43**, 356 (1910).

<sup>4</sup> R. Takamoto, *J. Pharm. Soc. Jpn.* **48**, 686 (1928).

<sup>5</sup> R. Takamoto, *J. Pharm. Soc. Jpn.* **48**, 872 (1928).

<sup>6</sup> D. B. Collum, S. C. Chen, and G. Bruce, *J. Org. Chem.* **43**, 4393 (1978).

<sup>7</sup> R. Littmann and C. S. Marvel, *J. Am. Chem. Soc.* **52**, 287 (1930).

<sup>8</sup> U.S. Patent 2,740,780 (1956) [*CA* **50**, 15598 (1956)].

<sup>9</sup> J. Diamond, W. F. Bruce, and C. Gochman, *J. Org. Chem.* **25**, 65 (1960).

<sup>10</sup> A. Müller and P. Bleir, *Monatsh. Chem.* **56**, 391 (1930).

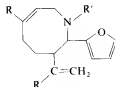
<sup>11</sup> A. Müller, E. Srepl, E. Funder-Fritzsche, and F. Dicher, *Monatsh. Chem.* **83**, 386 (1956).

<sup>12</sup> N. J. Leonard and R. C. Stentz, *J. Am. Chem. Soc.* **74**, 1704 (1952).

prepare other *N*-substituted azocinones.<sup>13-16</sup> The cyclooligomerization of 1,3-dienes with furfuraldimines in the presence of nickel complexes is reported to yield azacyclooctenes (16).<sup>17</sup> Schmutz and co-workers<sup>18</sup> have obtained small yields of the dicarbethoxy derivative 17 by condensing 1,4-dibromobutane with diethyl 2-(*N,N*-dimethylamino)ethylmalonate. Thermal cyclization of anil 18 gives rise to dihydroazocine 19.<sup>19</sup> Nitzschke and Budha<sup>20</sup> obtained 20 by cyclizing *N*-cyano-*N*-(6-cyanoheptyl)aniline with sodium *N*-methylanilide.

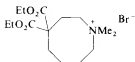


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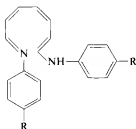


(16)

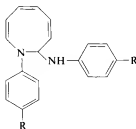
R = H, Me  
R' = Me, allyl



(17)



(18)



(19) R = H, Br



(20)

## 2. Via Ring Expansion

Perhaps the commonest ring expansion method of azocine synthesis is by Beckmann or Beckmann-type rearrangements of cycloheptanone

<sup>13</sup> N. J. Leonard, R. C. Fox, M. Oki, and S. Chiavarelli, *J. Am. Chem. Soc.* **76**, 630 (1954).

<sup>14</sup> N. J. Leonard, M. Oki, and S. Chiavarelli, *J. Am. Chem. Soc.* **77**, 6234 (1955).

<sup>15</sup> N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.* **80**, 4858 (1958).

<sup>16</sup> N. J. Leonard and T. Sato, *J. Org. Chem.* **34**, 1066 (1969).

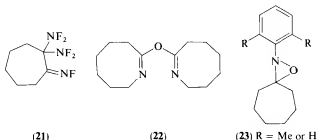
<sup>17</sup> U. M. Dzhemilev, L. Yu. Gubaidullin, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **11**, 2557 (1978) [*CA* **90**, 121386 (1978)].

<sup>18</sup> J. Schmutz, F. Kunzle, and R. Hirt, *Helv. Chim. Acta* **37**, 1762 (1954).

<sup>19</sup> L. A. Khanina, N. S. Pirnenko, V. Kh. Grif, N. E. Grigor'eva, and V. F. Lavrushin, *Zh. Obshch. Khim.* **45** 2471 (1975).

<sup>20</sup> H. J. Nitzschke and H. Budha, *Chem. Ber.* **88**, 264 (1955).

(suberone) oxime<sup>21-30</sup> and its substituted derivatives.<sup>31-35</sup> The lactams (e.g., **15**) can then be reduced using conventional methods. The cycloheptyl-fluorimine **21** undergoes a Beckmann-type rearrangement to give 3,3- and 8,8-bis(*N,N*-difluoroamino)enantholactams.<sup>36</sup> On reduction with lithium aluminum hydride, 1-nitro-1-methylcycloheptane yielded a small amount of 2-methylheptamethyleneimine, in addition to the tertiary cycloalkylamine.<sup>35</sup> Reduction of bisenantholactim ether (**22**), obtained by treatment of suberone oxime with  $\text{PCl}_5$ , resulted in octahydroazocine (**3**) and enantholactam (**15**).<sup>37</sup> Enantholactam is also formed from the reaction of *gem*-chloronitrosocycloheptane with triphenylphosphine.<sup>38</sup> Suberone oxime reacts with phosgene to form *N*-chloro-1,2,3,4,5,6-hexahydroazocine-2-



<sup>21</sup> German Patent 611,248 (1933) [*CA* **29**, 4134 (1933)].

<sup>22</sup> D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel, and F. J. Van Natta, *J. Polym. Sci.*, **3**, 85 (1948).

<sup>23</sup> Hungarian Patent 153,819 (1967) [*CA* **67**, 116824 (1967)].

<sup>24</sup> F. F. Blicke and N. J. Doorenbos, *J. Am. Chem. Soc.*, **76**, 2317 (1954).

<sup>25</sup> A. H. Beckett, *J. Pharm. Pharmacol.*, **8**, 860 (1956).

<sup>26</sup> British Patent 723,594 (1956) [*CA* **50**, 5737 (1956)].

<sup>27</sup> E. F. J. Duynstee, J. L. J. P. Hennekens, and M. E. A. H. Mevis, *Recl. Trav. Chim. Pays-Bas*, **84**, 1442 (1965).

<sup>28</sup> K. Smeykal, W. Pritzkow, G. Mahler, K. Krestschmann, and E. Ruehlmann, *J. Prakt. Chem.*, **30**, 126 (1965).

<sup>29</sup> Belgian Patent 616,354 (1963) [*CA* **58**, 12429 (1963)].

<sup>30</sup> Belgian Patent 616,909 (1962) [*CA* **57**, 14947 (1962)].

<sup>31</sup> A. Zabza, H. Kuczyński, Z. Chabudzinski, and G. Piotrowska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **21**, 1 (1973); A. Zabza, H. Kuczyński, Z. Chabudzinski, and D. Sedzik-Hibner, *ibid.*, **20**, 841 (1972).

<sup>32</sup> Z. Chabudzinski, D. Sedzik-Hibner, U. Lipnicka, and G. Piotrowska, *Rocz. Chem.*, **46**, 1089 (1972).

<sup>33</sup> C.-J. Jung and F. F. Blicke, *Hwa Hsueh Pao*, **22**, 513 (1956).

<sup>34</sup> A. A. Cervasco, *Diss. Abstr. B*, **29**, 532 (1968).

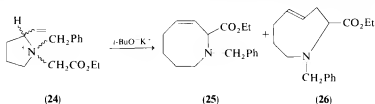
<sup>35</sup> H. J. Barber and E. Lunt, *J. Chem. Soc.*, 1187 (1960).

<sup>36</sup> T. E. Stevens, *J. Org. Chem.*, **34**, 2451 (1969).

<sup>37</sup> I. Beck, J. Rakoczi, and J. Torok, *Acta Chim. Acad. Sci. Hung.*, **75**, 63 (1972).

<sup>38</sup> M. Ohno and I. Sakai, *Tetrahedron Lett.*, (50), 4541 (1965).

carbonyl chloride.<sup>39</sup> *N*-Phenyl-substituted enantholactams have been prepared by the photolysis<sup>40</sup> and thermolysis<sup>41</sup> of oxaziridines such as **23**. Irradiation of  $\alpha$ -nitrocycloheptanone<sup>42</sup> or of  $\alpha$ -cyano- $\alpha$ -methylcyclohexanone<sup>43</sup> gives *N*-hydroxyperhydroazocine-2,8-dione and 2-methyl-3-methoxy-3,4,5,6,7,8-hexahydroazocine-8-one, respectively. *N*-Alkyl-substituted glutarimides undergo photocyclization to afford 6-ketoenantholactams with ring enlargement by the two-carbon unit derived from the side chain.<sup>44,45</sup> Three-carbon ring expansions have been reported by Vedejs and co-workers<sup>46</sup> who treated a mixture of diastereomers of *N*-benzyl-*N*-ethoxycarbonylmethyl-2-vinylpyrrolidinium bromide **24** with potassium *tert*-butoxide to give a mixture of the hexahydroazocine isomers **25** and **26**. Alkaline hydrolysis of 1-methyl-1-azoniabicyclo[4.2.0]octane chloride or its



acyclic precursor 2-(*N*-methyl-2-piperidyl)-1-chloroethane gave a small yield of *N*-methyloctahydroazocin-4-ol, in addition to the expected 2-(*N*-methyl-2-piperidyl)ethanol.<sup>47</sup> The only report of the formation of azocine (**4**) is by Hedaya and co-workers<sup>48</sup> who obtained mass spectral and chemical evidence for its production in the vacuum pyrolysis of the diazobasketene **27**. Similarly, Farnum and co-workers<sup>49</sup> postulated the intermediacy of  $\text{BF}_3$ -coordinated azocine *N*-oxide in the  $\text{BF}_3$ -catalyzed transformation of diazabasketene *N*-oxide to benzaldehyde oxime. Other unsaturated azocines have been made by thermal isomerization of the *cis*-aza- $\sigma$ -homobenzene **28** ( $X = p\text{-MeC}_6\text{H}_4\text{N}$ ,  $\text{NSO}_2\text{Me}$ ,  $\text{NSO}_2\text{C}_6\text{H}_4\text{Me}$ ) to the azocine **29**.<sup>50,51</sup>

<sup>39</sup> Netherland Patent Appl. 293,907 (1965) [*CA* **63**, 11524 (1965)].

<sup>40</sup> M. Fischer, *Tetrahedron Lett.* (27), 2281 (1969).

<sup>41</sup> M. Fischer, *Tetrahedron Lett.* (40), 4295 (1968); *Chem. Ber.* **102**, 342 (1969).

<sup>42</sup> S. T. Reid and J. N. Tucker, *J. Chem. Soc. D*, 1609 (1971).

<sup>43</sup> G. K. Chip and T. R. Lynch, *J. C. S. Chem. Commun.* (17), 641 (1973).

<sup>44</sup> Y. Kanaoka and Y. Hatanaka, *J. Org. Chem.* **41**, 400 (1976).

<sup>45</sup> Y. Kanaoka, H. Okajima, and Y. Hatanaka, *Heterocycles* **8**, 339 (1977).

<sup>46</sup> E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.* **43**, 1185 (1978).

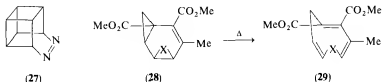
<sup>47</sup> A. Ebnoether and E. Jucker, *Helv. Chim. Acta* **47**, 745 (1964).

<sup>48</sup> D. W. McNeil, M. E. Kent, E. Hedaya, P. F. D'Angelo, and P. O. Schissel, *J. Am. Chem. Soc.* **93**, 3817 (1971).

<sup>49</sup> J. P. Snyder, L. Lee, and D. G. Farnum, *J. Am. Chem. Soc.* **93**, 3816 (1971).

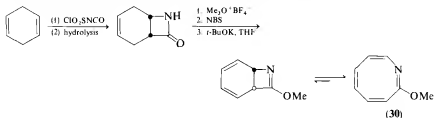
<sup>50</sup> D. Stusche, M. Breuninger, and H. Prinzbach, *Helv. Chim. Acta* **55** (7), 2359 (1972).

<sup>51</sup> H. Prinzbach, D. Stusche, J. Markert, and H. H. Limbach, *Chem. Ber.* **109**, 3505 (1976).



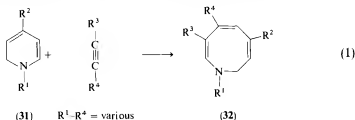
### 3. Via Cycloaddition and Cycloreversion

Paquette and co-workers<sup>52,53</sup> prepared 2-methoxyazocine (30) by the method in Scheme 1. A number of alkyl-2-methoxyazocines have also been



SCHEME 1

made using this synthetic approach. Dihydroazocines **32** can be made from 1,2-dihydropyridines **31** and substituted acetylenes, e.g., Eq. (1).<sup>54-58</sup> A



similar type of reaction is undergone by 1-methyl-4-pyrrolidino-4-azacyclohex-1-ene<sup>59</sup> and by 2-pyridones.<sup>60</sup> Condensation of nicotinamide derivative

<sup>52</sup> L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.* **90**, 3897 (1968).

<sup>53</sup> L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Am. Chem. Soc.* **93**, 152 (1971).

<sup>54</sup> R. M. Acheson, G. Paglietti, and P. A. Tasker, *J. C. S. Perkin I* (21), 2496 (1974).

<sup>55</sup> R. M. Acheson and G. Paglietti, *J. C. S. Chem. Commun.* (18), 665 (1973).

<sup>56</sup> P. S. Mariano, M. E. Osborn, and E. Krochmal, Jr., *Tetrahedron Lett.* (32), 2741 (1975).

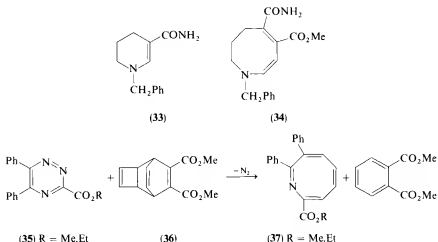
<sup>57</sup> P. S. Mariano, M. E. Osborn, D. Dunaway-Mariano, B. C. Gunn, and R. C. Peterson, *J. Org. Chem.* **42**, 2903 (1977).

<sup>58</sup> Private communication from P. S. Mariano, L. Yerin, and M. E. Osborn.

<sup>59</sup> D. N. Reinhoudt and C. G. Kourvenhoven, *Tetrahedron Lett.* (39), 3751 (1973).

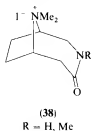
<sup>60</sup> K. Somekawa, T. Shimou, K. Tanaka, and S. Kumamoto, *Chem. Lett.*, 45 (1975).

**33** with methyl acetylenecarboxylate gives azocine **34**.<sup>61</sup> Triazines **35** react with the cyclobutene **36** in a [4 + 2] cycloaddition followed by fragmentation to **37**.<sup>62,63</sup>



#### 4. Miscellaneous

Enantholactone is converted into enantholactam by treatment with hydrogen and ammonia under pressure in the presence of a catalyst.<sup>64</sup> The Hofmann elimination of the diazabicyclo compound **38** has been found to afford unsaturated azocinones.<sup>65,66</sup> Nagasawa and Eberling<sup>67</sup> have reported



<sup>61</sup> R. M. Acheson and G. Paglietti, *Heterocycles* **12** 695 (1979).

<sup>62</sup> J. A. Elix, W. S. Wilson, and R. N. Warrener, *Tetrahedron Lett.* (21), 1837 (1970).

<sup>63</sup> J. A. Elix, W. S. Wilson, R. N. Warrener, and I. C. Calder, *Aust. J. Chem.* **25** (4), 865 (1972).

<sup>64</sup> U. S. Patent 2,817,646 (1957) [*CA* **52**, 7348 (1957)].

<sup>65</sup> L. A. Paquette and L. D. Wise, *J. Org. Chem.* **30**, 228 (1965).

<sup>66</sup> L. A. Paquette and L. D. Wise, *J. Am. Chem. Soc.* **87**, 1561 (1965).

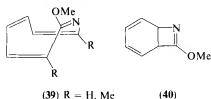
<sup>67</sup> H. T. Nagasawa and J. A. Elberling, *Tetrahedron Lett.* (44), 5393 (1966).

the synthesis of heptamethyleneimine (**3**) via the Favorskii-type rearrangement of  $\alpha$ -halogenated nine-membered lactams.

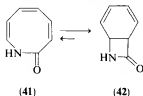
## B. THEORETICAL ASPECTS

Azocine (**4**), even before its detection by Hedaya,<sup>48</sup> was of theoretical interest because it is a heterocyclic analog of the  $8\pi$  nonaromatic annulene cyclooctatetraene (COT). Although azocine itself was found to be quite unstable, earlier work by Paquette and co-workers<sup>52,53</sup> on the synthesis of azocine derivatives indicated that appropriately substituted compounds could be more stable. Paquette<sup>68</sup> has recently reviewed the chemistry of these compounds. The picture of azocine vis a vis cyclooctatetraene<sup>68a</sup> is outlined below.

1. Methylated and unmethylated methoxyazocine appear, on the basis of their chemistry and spectroscopy, to exist in the tub conformation (**39**), similar to cyclooctatetraene. These compounds react with dienophiles and potassium *t*-butoxide to give Diels-Alder adducts and benzonitriles, respectively, presumably via an azabicyclo[4.2.0]octane isomer (**40**). The properties of **39** indicate that the methoxy group is attached to the imino and not an olefinic carbon. This has been confirmed by recent *ab initio* calculations.<sup>69</sup>



2. The eight-membered ring lactam **41**, in contrast to the azocines themselves, exist mainly as the bicyclic  $\beta$ -lactam **42**.

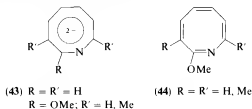


<sup>68</sup> L. A. Paquette, *Khim. Geterotsikl. Soedin.* (2), 147 (1978); *Chem. Heterocycl. Compd.* **14** (2), 111 (1978).

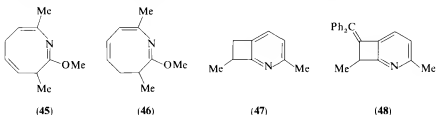
<sup>68a</sup> G. Schröder, "Cyclooctatetraen." Verlag Chemie, Weinheim, 1965; G. I. Fray and R. G. Saxton, "The Chemistry of Cyclooctatetraene and its Derivatives." Cambridge Univ. Press, London and New York, 1978.

<sup>69</sup> A. Greenberg and R. Winkler, *J. Mol. Struct.* **63**, 131 (1980).

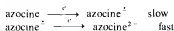
3. The  $\pi$ -energy levels of a hypothetical flat azocine (**4**) were compared with those of the COT analog. The relative ease of two-electron reduction was compared. The flat cyclooctatetrene dianion has a delocalization energy (DE) of  $-3.7 \beta$ , while a flat azocinyl dianion (**43a**) has a DE of about  $-5.1 \beta$ . Indeed, methoxyazocine and its methylated derivatives (**44**) are readily reduced to the corresponding dianions **43b**.



4. Protonation of azocinyl dianion **43** ( $R = R' = Me$ ) led to the dihydro species **45** and **46**, the latter compound providing an entry into the cyclobutenopyridine **47**. Treatment of the same azocinyl dianion with benzophenone resulted in incorporation of the benzhydryl moiety and eventual formation of **48**, a reaction not observed with COT dianion.



5. The COT and azocinyl dianions evinced contrasting electrochemical behavior. Whereas COT underwent two nearly Nernstian one-electron reductions, the azocines gave a single reduction wave, the diffusion current indicating an overall two-electron transfer.

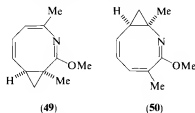


The azocines **44** thus hold the unique position of being the first  $4n\pi$ -electron system capable of electrochemical multielectron addition at the discharge potential. Paquette attributed this to a combination of steric and electronic factors that favor the ring-flattening process more than that for COT. However, Jensen and co-workers<sup>70</sup> have recently questioned this conclusion. They found the electrochemical behavior of **44** dependent on the size of the counterion used.

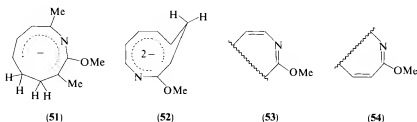
<sup>70</sup> B. S. Jensen, T. Petterson, A. Ronlan, and V. D. Parker, *Acta Chem. Scand., Ser. B* **B30** 773 (1976)



6. Paquette and co-workers<sup>68,71</sup> also investigated the chemistry of homologs of methoxyazocine. For example, dimethylmethoxyazocine **44** ( $R = R' = \text{Me}$ ), undergoes cyclopropanation upon treatment with  $\text{CH}_2\text{Cl}_2$  to give isomeric homoazocines **49** and **50**. The former is reduced to give azoninyl



anion **51**, raising the possibility that a homoaromatic anion related to **52** intervenes in the conversion. Reduction of homoazocine **50** afforded only unchanged starting material when subjected to conditions similar to those for **49**.<sup>71</sup> The polarographic reduction of **49** and **50** was also examined. Replacement of a double bond by a fused cyclopropane results in a decrease in the ease of electrochemical reduction, the  $\Delta E_{1/2}$  value being considerably larger than those found for the related COT-homo-COT pair. Therefore any latent homoaromaticity of 9C-10 $\pi$  dianions had not been enhanced by heteroatom substitution. The fact that electrochemical reduction of **50** occurs more readily than that of **49** is attributed to the capability of the imino ether linkage to function systematically either as an electron-rich olefin (**53**) or as an electron-withdrawing substituent (**54**), depending upon its bonding orientation within the cyclic framework.

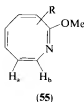


### C. STEREOCHEMISTRY

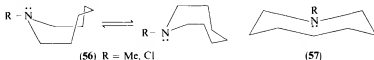
Most of the stereochemical studies of azocines have been concerned with the fully saturated compound **3** and enantholactam (**15**) and their derivatives, the work on the unsaturated system **44** having been done by Paquette and

<sup>71</sup> L. A. Paquette, G. B. Ewing, S. V. Ley, H. C. Berk, and S. G. Traynor, *J. Org. Chem.* **43**, 4712 (1978).

co-workers.<sup>68</sup> The spectral and chemical properties of methoxyazocine were best explained if the azocine existed in a tub-shaped conformation (**39**) similar to that of COT itself. The UV spectra of **39** and COT were similar.<sup>68a</sup> Presumably the unsubstituted azocine itself has a similar shape. The proton NMR spectrum of **55** was temperature-invariant from  $-75^{\circ}$  to  $185^{\circ}\text{C}$ , which seemed to indicate the absence of any valence-bond isomerization of the type present in COT.



Lambert and Khan<sup>72</sup> examined the temperature-dependent 270 MHz proton and 22.0 MHz  $^{13}\text{C}$ -NMR spectra of perhydroazocine (**3**) and concluded that the preferred shape is a boat chair (**56**), with a boat-chair  $\rightleftharpoons$  boat-chair barrier of 8–9 kcal/mol. They found evidence for hindered ring reversal but none for hindered nitrogen inversion, even though the latter barrier is not low. Anet and co-workers<sup>73</sup> found a slightly lower boat-chair barrier of 7.3 kcal/mol (compared with that of 7.4 kcal/mol for oxacyclooctane and 8.1 kcal/mol for cyclooctane). They found a dynamic  $^{13}\text{C}$ -NMR effect, but claimed that it arose not from boat-chair  $\rightleftharpoons$  boat-chair ring inversion, but rather from boat-chair (**56**)  $\rightleftharpoons$  crown (**57**) interconversion. The



crown population was estimated to be 3%. The  $\Delta G$  for these processes was found to be 1.2 and 10.5 kcal/mol respectively, as compared with 1.7 kcal and 10.5 kcal/mol, respectively, for cyclooctane. Using ESR, Hudson and Hussain<sup>74</sup> estimated an  $E_{act}$  of 9.5 kcal/mol for ring inversion of **58**. The



<sup>72</sup> J. B. Lambert and S. A. Khan, *J. Org. Chem.* **40**, 369 (1975).

<sup>73</sup> F. A. L. Anet, P. J. Degen, and I. Yavari, *J. Org. Chem.* **43**, 3021 (1978).

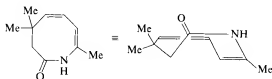
<sup>74</sup> A. Hudson and H. A. Hussain, *J. Chem. Soc. B*, 1346 (1968).

properties of perhydroazocine, compared to its smaller and larger homologs (**59**,  $X = NH$ ), roughly parallel the relative behavior of cyclooctane in the carbocyclic series (**59**,  $X = CH_2$ ).<sup>75</sup> A combination of factors, including Baeyer and Pitzer strain in the ground and transition states, are responsible for these trends. Perhydroazocine demonstrated similar behavior in its reaction with *p*-fluoronitrobenzene.<sup>76</sup>



The perhydroazocine ring is ideally suited for intramolecular reactions involving transannular interactions. Cope and LeBel<sup>77</sup> found that *N*-methylperhydroazocine *N*-oxide underwent pyrolytic elimination much more readily than smaller ring homologs, consistent with a planar five-membered transition state. Leonard and co-workers<sup>78</sup> found a very strong transannular interaction in perhydroazocine-5-ones (**60**) that was attenuated by the presence of bulky or electron-withdrawing substituents on the nitrogen. The presence of a chiral nitrogen substituent led to a dissymmetrically perturbed symmetric chromophore and resulted in an anomalous ORD curve for the optically active amino ketone.<sup>79</sup>

Most studies on eight-membered lactams have been on the completely saturated system (**15**). However, compound **61** showed an NMR spectrum



<sup>75</sup> L. Ruzicka, M. Kobett, O. Hafliger, and V. Prelog, *Helv. Chim. Acta* **32** 544 (1979); M. Havel, J. Krupicka, M. Svoboda, J. Zavada, and J. Sicher, *Collect. Czech. Chem. Commun.* **33**, 1429 (1968), and references cited therein; J. D. Dunitz and V. Prelog, *Angew. Chem.* **72**, 896 (1960).

<sup>76</sup> A. Fischer, R. E. J. Hutchinson, R. D. Topsom, and G. J. Wright, *J. Chem. Soc. B*, 544 (1969).

<sup>77</sup> A. C. Cope and N. A. LeBel, *J. Am. Chem. Soc.* **82**, 4656 (1960).

<sup>78</sup> N. J. Leonard, M. Oki, and S. Chiavarelli, *J. Am. Chem. Soc.* **77**, 6234 (1955); N. J. Leonard and M. Oki, *ibid.* p. 6239, 6241, 6245.

<sup>79</sup> N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.* **80**, 4858 (1958).

that indicated its existence as two planar, enantiomeric forms, presumably tub-shaped.<sup>80</sup> On the basis of heats of combustion, enantholactam is more strained than smaller ring homologs, the order of stability being five > six > seven > eight.<sup>81</sup> However, the heats of hydrolysis for these same four lactams was reported as following an order that indicated a reverse order of stability.<sup>82</sup> Similarly, the rate of polymerization of enantholactam was less than that of caprolactam.<sup>83</sup> However, the infrared carbonyl stretching frequencies for six-, seven-, and eight-membered lactams were essentially identical ( $1605 \pm 1 \text{ cm}^{-1}$ ).<sup>84</sup> This was taken to indicate that the IR frequencies are dependent on hybridization, not angle strain. Infrared,<sup>84-86</sup> nuclear magnetic resonance,<sup>86,87,87a</sup> and molecular polarization studies<sup>87a</sup> of enantholactam and its *N*-methyl derivative indicated that the eight-membered ring was too small to allow for the *s-trans*-amide configuration without excessive transannular proton crowding. Thus, enantholactam is the largest lactam to exist exclusively in the *cis* form. The nine-membered lactam exists as a mixture of tautomers, mainly as *cis* while the 10-membered homolog exists mainly as *trans*. This was also borne out by X-ray diffraction studies, which also indicated expanded internal angles, as compared with normal values, in order to relieve puckering and alleviate transannular repulsions.<sup>88</sup> Infrared studies on the thioenantholactam showed it to be in the *cis* configuration as compared with the nine-membered ring homolog which exists as *trans*.<sup>89</sup> NMR studies suggested that the thiolactam existed in part in a crown conformation in addition to the expected boat form.

<sup>80</sup> A. Zabza, H. Kuczynski, Z. Chabudzinski, and D. Sedzik-Hibner, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **20**, 841 (1972) [*CA* **78**, 124728 (1973)].

<sup>81</sup> O. N. Kachinskaya, *Zh. Fiz. Khim.* **30**, 235 (1956) [*CA* **50**, 12627 (1956)]; A. A. Strepikheev, S. M. Skuratov, O. N. Kachinskaya, R. S. Muronova, E. P. Brykina, and S. M. Shtekher, *Dokl. Akad. Nauk SSSR* **102**, 105 (1955) [*CA* **50**, 4903 (1956)].

<sup>82</sup> A. K. Bonetskaya, N. F. Erofeera, and S. M. Skuratov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **3**, 1027 (1960) [*CA* **65**, 16411 (1966)]; A. K. Bonetskaya, N. F. Erofeera, S. M. Skuratov, and R. S. Muronova, *ibid.* **4**, 74 (1961) [*CA* **55**, 15071 (1961)]; A. A. Strepikheev and R. S. Muronova, *Khim. Nauka Prom-st.* **2**, 395 (1957) [*CA* **52**, 257 (1958)]; B. Coutin and H. Sekiguchi, *C. R. Hebd. Seances Acad. Sci., Ser. C* **268**, 2281 (1969).

<sup>83</sup> R. C. P. Cubbon, *Polymer* **4**, 545 (1963).

<sup>84</sup> H. K. Hall, Jr. and R. Zbinden, *J. Am. Chem. Soc.* **80**, 6428 (1958).

<sup>85</sup> M. V. Shablygin, D. N. Shigorin, and N. V. Mikhailov, *Zh. Prikl. Spektrosk.* **3**, 56 (1965) [*CA* **64**, 5939 (1965)]; H. E. Hallam and C. M. Jones, *J. Mol. Struct.* **1**, 413, 425 (1968).

<sup>86</sup> R. Huisgen, H. Brock, H. Walz, and I. Glogger, *Chem. Ber.* **90**, 1473, (1957).

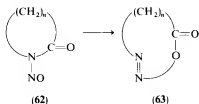
<sup>87</sup> R. M. Moriarty and J. M. Kliegman, *J. Org. Chem.* **31**, 3007 (1966); *Tetrahedron Lett.*, 891 (1966).

<sup>87a</sup> R. Huisgen and H. Walz, *Chem. Ber.* **89**, 2616 (1956).

<sup>88</sup> T. K. Winkler and J. D. Dunitz, *J. Mol. Biol.* **59**, 169 (1971).

<sup>89</sup> H. E. Hallam and C. M. Jones, *J. Chem. Soc. A*, 1033 (1969).

Huisgen and Reinertshofer<sup>90</sup> studied the rearrangement of *N*-nitroso-lactams of varying ring size (**62**), to the corresponding diazoesters **63** and found that the *N*-nitrosoenantholactam (**62**,  $n = 6$ ) reacted faster than smaller rings, but slower than the nine-membered homolog. The order of reactivity was attributed to the relative ease in attaining a four-membered transition state required for formation of the *trans*-azo group, which is the preferred stereochemistry.

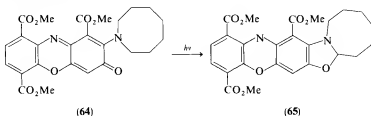


## D. REACTIONS

This section deals primarily with the reactions of derivatives of partially and fully saturated eight-membered rings, including enantholactam (**15**). Those that are of particular relevance to the azocine ring, such as *trans*-annular reactions, will be discussed in somewhat greater detail.

### 1. Eight-Membered Ring Preserved

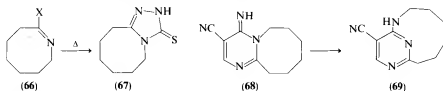
a. *Annellation*. 2-(1-Heptamethyleneimino)-3*H*-phenoxazin-3-one (**64**), prepared from the corresponding 2-chloro-3*H*-phenoxazine-3-one and heptamethyleneimine (perhydroazocine), underwent photochemical ring closure to the pentacyclic **65**, most likely via formation of an iminium ion by hydrogen transfer from the excited quinone carbonyl and addition to a quinone hydrate.<sup>91</sup>



<sup>90</sup> R. Huisgen and J. Reinertshofer, *Justus Liebigs Ann. Chem.* **575**, 174 (1952).

<sup>91</sup> M. C. Wani and S. G. Levine, *J. Org. Chem.* **31**, 2564 (1966).

Enantholactam (**15**) could be converted to the dithiocarbazinic ester **66** ( $X = \text{NHNHCS}_2\text{R}$ ) via the lactim ether **66**, ( $X = \text{OCH}_3$ ). The ester, upon heating, underwent ring closure to the 3-mercapto-4,5-hexamethylene-1,2,4-triazole (**67**).<sup>92</sup> Enantholactim ethyl ether (**66**,  $X = \text{OC}_2\text{H}_5$ ) underwent cycloaddition with aminoethylenemalononitrile to give the iminopyrimidoazocine **68**, which reacted to give the  $\beta$ -bridged **69** via a Dimroth rearrangement.<sup>93</sup> Smaller ring azaheterocycles failed to give the pyrimido adduct.



$X = \text{OR}$

$X = \text{NHNHCS}_2\text{R}$

b. *Reactions at Nitrogen.* Examples of alkylations are: reactions with ketones to form enamines,<sup>94</sup> Mannich reaction with acetovanillone and formaldehyde,<sup>95,96</sup> reaction with haloalcohols and haloesters,<sup>96</sup> 2-chloroethylamine,<sup>97</sup> with phenacyl bromides,<sup>95</sup> chloromethyl methyl ether,<sup>98</sup> tosylates<sup>99</sup> and mesylates,<sup>100</sup> ring opening of styrene oxide<sup>101</sup> and ethyleneimine.<sup>102</sup> A typical synthesis of the pharmacologically important 1-[*N*-azacyclooctyl]ethyl]-2-guanidine sulfate (Section II,E) is the conversion of perhydroazocine to the *N*-cyanomethyl derivative by either cyanomethylation<sup>103</sup> or Knoevenagel condensation,<sup>104</sup> followed by condensation with *S*-methylisothiourea sulfate.<sup>104</sup> Other methods<sup>105</sup> vary, but all begin

<sup>92</sup> J. Korosi and P. Berencsi, *Chem. Ber.* **101**, 1979 (1968).

<sup>93</sup> D. J. Drown and K. Ienaga, *Aust. J. Chem.* **28**, 119 (1975).

<sup>94</sup> G. A. Stork, A. Brizzolara, H. Landesman, and J. Szmzykovicz, *J. Am. Chem. Soc.* **85**, 207 (1963).

<sup>95</sup> F. F. Blicke and W. J. Johnson, *J. Am. Pharm. Assoc., Sci. Ed.* **45**, 440 (1956) [*CA* **51**, 1209 (1957)].

<sup>96</sup> N. J. Doorenbos, *Diss. Abstr.* **14**, 603 (1954).

<sup>97</sup> A. I. Adamovich, E. I. Boksinen, A. Grigor'eva, G. N. P'yankova, and I. K. Fel'dman, *Khim.-Farm. Zh.* **1**, 18 (1967) [*CA* **69**, 35912 (1968)].

<sup>98</sup> German Patent 1,074,045 (1960) [*CA* **55**, 13454 (1961)].

<sup>99</sup> French Patent 1,511,193 (1968) [*CA* **71**, 3120 (1969)].

<sup>100</sup> Hungarian Patent 150,598 (1961) [*CA* **60**, 5516 (1964)].

<sup>101</sup> W. Ziegenbein and W. Franks, *Chem. Ber.* **90**, 2291 (1957).

<sup>102</sup> French Patent 1,336,403 (1963) [*CA* **60**, 2917 (1964)].

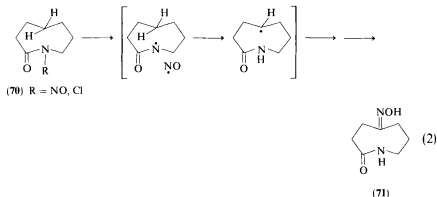
<sup>103</sup> O. M. Lerner and I. K. Fel'dman, *Zh. Prikl. Khim.* **36**, 1347 (1963) [*CA* **59**, 10041 (1963)].

<sup>104</sup> I. K. Fel'dman and O. M. Lerner, *Med. Prom-st. SSSR* **16**, 16 (1962) [*CA* **58**, 4521 (1963)].

<sup>105</sup> U.S. Patent 2,928,829 (1960) [*CA* **54**, 17436 (1960)], S. Fila-Hromadko, *Croat. Chem. Acta* **36**, 99 (1964) [*CA* **61**, 14639 (1964)].

with perhydroazocine. Acylations include reactions with sulfonyl chlorides,<sup>106</sup> chloroacetyl chloride,<sup>107</sup> and nicotinoyl chloride.<sup>108</sup> Formation of N—N compounds include nitrosation,<sup>109,110</sup> usually followed by reduction<sup>109</sup> and sulfonation at the primary amine.<sup>110,111</sup>

c. *Reactions between Nitrogen and Transannular Carbon.* These reactions, usually unique to the perhydroazocine system, involve reaction at transannular carbon (usually C-5 but to lesser extent C-4), transannular N—C-5 migration and N—C-5 closure to the 1-azabicyclo[3.3.0]octane (pyrrolizidine) system. This latter reaction is especially important as a route to mitomycins (see Sections III,A and D). Irradiation of *N*-nitroso-2-azacyclooctanone (**70**, R = NO) produced 6-oximino-2-azacyclooctanone (**71**) via 1,5-transannular hydrogen migration (Eq. 2).<sup>112</sup> Similarly, *N*-



chloroazacyclooctan-2-one (**70**, R = Cl) underwent peroxide-initiated photochemical conversion to 5-chloroazacyclooctane-2-one.<sup>113</sup> Under "ionic" conditions, **70** (R = Cl) yielded mainly parent lactam plus a trace of bicyclic product **72**; in contrast, the nine-membered homolog gave bicyclic products under both free radical and ionic conditions. Microbiological oxygenation

<sup>106</sup> S. Fila-Hromadko, B. Gluncic, and D. Kolbah, *Croat. Chem. Acta* **39**, 207 (1967) [*CA* **68**, 68867 (1968)]; *ibid.* p. 289 [*CA* **69**, 2854 (1968)].

<sup>107</sup> S. Binecki and K. Niewiakowski, *Acta Pol. Pharm.* **26**, 1 (1969) [*CA* **71**, 22028 (1969)].

<sup>108</sup> S. Binecki and A. Giro, *Acta Pol. Pharm.* **27**, 521 (1970) [*CA* **74**, 99828 (1971)]; **28**, 137 (1971) [*CA* **75**, 76589 (1971)].

<sup>109</sup> R. Takamoto, *J. Pharm. Soc. Jpn.* **48**, 686 (1928) [*CA* **23**, 387 (1929)].

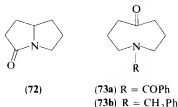
<sup>110</sup> Belgian Patent 610,039 (1962) [*CA* **58**, 1469 (1963)].

<sup>111</sup> Swiss Patent 436,288 (1967) [*CA* **69**, 10473 (1968)].

<sup>112</sup> O. E. Edwards and R. S. Rosich, *Can. J. Chem.* **45**, 1287 (1967).

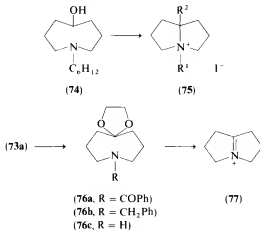
<sup>113</sup> O. E. Edwards, J. M. Paton, M. H. Benn, R. E. Mitchell, and C. Watanatada, *Can. J. Chem.* **49**, 1648 (1971), and references cited therein.

of *N*-benzoylheptamethyleneimine resulted in a crude mixture that could be oxidized to give mainly **73** plus a small amount of the isomeric 4-ketone.<sup>114</sup>



## 2. Ring Contraction

Most examples of ring contraction of eight-membered nitrogen heterocycles involve 1,5-transannular C–N closure to give the 1-azabicyclo[3.3.0]-octane (pyrrolizidine) system.<sup>115</sup> For example, treatment of *N*-cyclohexyl-1-azacyclooctane-5-ol (**74**), with acid gave *N*-cyclohexyl-1-azabicyclo[3.3.0]-octane iodide (**75**, R<sup>1</sup> = C<sub>6</sub>H<sub>12</sub>, R<sup>2</sup> = H).<sup>115</sup>



SCHEME 2

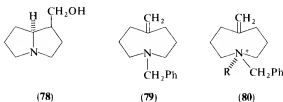
The reaction sequence **73a** → **77** (Scheme 2) was claimed as a new route to imminium salts, and the first entry into transannular reactions of secondary amines. Compounds **76a** (R = COPh) and **76b** (R = CH<sub>2</sub>Ph), can also

<sup>114</sup> French Patent 1,478,263 (1967) [CA 67, 107397 (1967)]; R. A. Johnson, M. E. Herr, H. C. Moway, and G. S. Fonken, *J. Org. Chem.* **33**, 3187 (1968).

<sup>115</sup> A. J. Sisti and D. L. Sohner, *J. Org. Chem.* **32**, 2026 (1967).



be converted to **75** ( $R^1 = \text{CH}_2\text{Ph}$ ,  $R^2 = \text{OH}$ ). Similarly, transannular reaction provided a route for stereospecific synthesis of the pyrrolizidine (Senecio) alkaloid ( $\pm$ )-isotretronecanol (**78**).<sup>16</sup> When **76d** ( $R = \text{CH}_2\text{CN}$ ), was treated with perchloric acid in aqueous ethanol, the bicyclic salt **75** ( $R^1 = \text{CH}_2\text{CN}$ ,  $R^2 = \text{OCH}_2\text{CH}_2\text{OH}$ ) was obtained.<sup>116</sup> The  $\text{CH}_2\text{CN}$  group apparently attenuated the basicity of the nitrogen sufficiently so as to permit the ketal oxygen to be protonated and thus allow the free amine to attack the proximate ketal carbon. Compound **79**, prepared from **73b**, was found to undergo both transannular and normal reactions, giving **75** ( $R^1 = \text{CH}_2\text{Ph}$ ,  $R^2 = \text{Me}$ ) and **80** ( $R = \text{H}$ ) with aqueous perchloric acid and only **80** ( $R = \text{Me}$ ) with methyl iodide.



When 1-aza-4-cyclooctene was treated with various electrophiles, pyrrolizidines **81** were formed.<sup>117</sup> A reaction mechanism proceeding via transannular attack by nitrogen was postulated. The 1-aza-4-cyclooctene-8-one did not undergo ring contraction on bromination and yielded the ordinary dibromolactam.



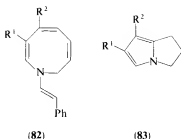
(81)  $X = \text{Br, I, HgCl, SePh, SPh}$

As part of a synthetic approach to the mitomycins (see Section II,A, III,A and D), Mariano and co-workers<sup>57,58</sup> prepared a series of dihydroazocines (**32**) (see Section II,A). *N*-Styryl derivatives of these compounds (**82**) were converted to pyrrolizidines **83** by a sequence which includes oxidative cleavage of the styryl group, reduction to a diene and epoxidation. Whereas **84** ( $n = 6$ ) on acid treatment, gave **85**, the perhydroazocinyl homolog **84** ( $n = 7$ ) afforded ring-contracted product **86**.<sup>118</sup> Perregaard and colleagues

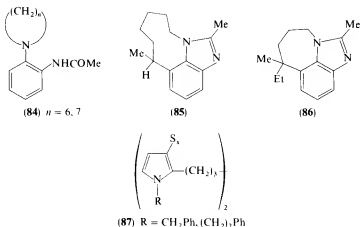
<sup>116</sup> R. A. Johnson, *J. Org. Chem.* **37**, 312 (1972), and references cited therein.

<sup>117</sup> S. R. Wilson and R. A. Sawicki, *J. Org. Chem.* **44**, 287 (1979).

<sup>118</sup> R. Garner and H. Suschitzky, *J. Chem. Soc. C*, 1572 (1966).



found that heating *N*-benzyl- and *N*-(2-phenylethyl)octahydroazocine with hexamethylphosphoramide containing suspended sulfur afforded bispyrrolyl polysulfides **87**.<sup>119</sup>

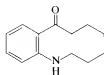


### 3. Ring Expansion

*N*-Phenylantholactam underwent photochemical ring enlargement to give **88**. Photolysis of *N*-(2,6-dimethylphenyl)antholactam resulted only in resinification.<sup>41</sup> Enantholactam (**15**) was used as the starting material for a series of reactions involving ring expansion by way of a Beckmann rearrangement to the cyclic urea **89** and eventual formation of **90**, the smallest known cyclic carbodiimide.<sup>120</sup>

<sup>119</sup> J. Perregaard, S. Schejbye, H. J. Meyer, I. Thomsen, and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **86**, 679 (1977).

<sup>120</sup> H. Behniger and H. Meier, *Justus Liebigs Ann. Chem.* **607**, 67 (1957).



(88)



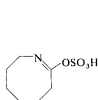
(89)



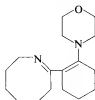
(90)

#### 4. Ring Opening

Enamines acylate lactim sulfonates, among them **91**, to yield lactimenes, exemplified by **92**.<sup>121</sup> The latter compound provided a route to  $\omega$ -aminocarboxylic acids via  $\omega$ -aminoketo acids. For example, beginning with **91**, one can prepare  $\omega$ -aminododecanoic acid.<sup>121a</sup>



(91)



(92)

2-Substituted-*N*-carbonyl-aza-2-cyclooctenes are convenient intermediates in the synthesis of amino acids.<sup>122-124</sup> These compounds, prepared from enantholactam, react with electrophiles to give  $\alpha$ -substituted enantholactams which then undergo reductive cleavage to give  $\alpha$ -substituted  $\omega$ -amino acids.

Pyrazine **93** was prepared by reductive cyclodimerization of 2-nitromethylenehexahydroazocine.<sup>125</sup> *o*-(1-Perhydroazocinyl)acetophenone was ring opened by Hg(II)(EDTA) to the aminoaldehyde **94**.<sup>126</sup> The reaction probably proceeds via *N*-aryliminium ions in a manner similar to that of photocyclization of **64**. Mercuric acetate oxidation of *N*-methylperhydroazocine, followed by HCl and H<sub>2</sub>S, afforded trithiane (**95**).<sup>127</sup> This was

<sup>121</sup> S. Hünig, E. Lücke, V. Meuer, and W. Grässmann, *Angew. Chem., Int. Ed. Engl.* **2**, 213 (1963); S. Hünig, W. Grässmann, V. Meuer, and E. Lücke, *Chem. Ber.* **100**, 3024 (1967).

<sup>121a</sup> S. Hünig, W. Grässmann, V. Meuer, E. Lücke, and W. Brenninger, *Chem. Ber.* **100**, 3039 (1967).

<sup>122</sup> German Patent 1,902,842 (1969) [*CA* **72**, 21623 (1970)].

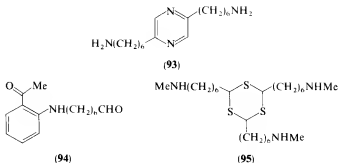
<sup>123</sup> German Patent 1,154,118 (1963) [*CA* **60**, 2789 (1964)].

<sup>124</sup> U.S. Patent 3,093,635 (1963) [*CA* **59**, 11272 (1963)].

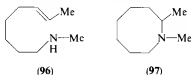
<sup>125</sup> S. Rajappa and R. Sreenivasan, *Tetrahedron Lett.*, 2217 (1978).

<sup>126</sup> H. Mochrlé and J. Gerloff, *Arch. Pharm. (Weinheim, Ger.)* **312**, 219 (1979).

<sup>127</sup> N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.* **81**, 5631 (1959).



thought to arise via the iminium salt which then ring opens to an  $\omega$ -amino aldehyde. Subsequent reaction of the aldehyde gives **95**. Clemmensen and Wolff-Kishner reductions of 1,2-dimethyl-1-azacyclooctane-3-one proceeded anomalously to give *n*-octylmethylamine and a mixture of **96** and **97**, respectively.<sup>12</sup> The formation of a ring-opened Clemmensen reduction product, as opposed to a ring-contracted one, seemed to indicate initial  $C_x-N$  cleavage prior to reduction of the ketone.



## E. APPLICATIONS

### 1. Pharmacological

Azocine derivatives are reported to exhibit hypnotic and anticonvulsive action<sup>128,129</sup> as well as central nervous system stimulation.<sup>130-136</sup> *N*-Propionyl-[1-(octahydroazocin-1-yl)isopropyl-2-aminopyridine was one of

<sup>128</sup> Netherland Patent 6,414,062 (1965) [*CA* **63**, 17989 (1965)].

<sup>129</sup> French Patent 1,581,285 (1970) [*CA* **73**, 25143 (1970)].

<sup>130</sup> E. J. Lien, L. L. Lien, and G. L. Tong, *J. Med. Chem.* **14**, 846 (1971).

<sup>131</sup> E. Elison, E. J. Lien, A. P. Zinger, M. Hussain, G. L. Toth, and M. Golden, *J. Pharm. Sci.* **60** (7), 1058 (1971).

<sup>132</sup> E. Palosi, C. Mezaros, and L. Szporny, *Arzneim.-Forsch.* **19** (11), 1882 (1969).

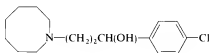
<sup>133</sup> L. Szporny and E. Palosi, *Orros Tudomany* **19** (3-4), 379 (1969).

<sup>134</sup> E. Palosi, L. Szporny, and K. Nador, *J. Pharm. Sci.* **57** (4), 709 (1968).

<sup>135</sup> T. Shimizu, H. Hamakawa, T. Tozuka, and T. Shimizu, *Nippon Yakurigaku Zasshi* **72** (7), 837 (1976).

<sup>136</sup> A. Linquist, S. Lindgren, B. Lindeke, B. Karlen, R. Dahlborn, and M. R. Blair, Jr., *Acta Pharm. Suec.* **9** (2), 93 (1972).

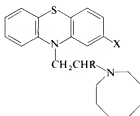
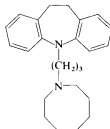
a number of *N*-(alkyleneiminoalkyl)aminopyridines which show analgesic properties.<sup>137,138</sup> The  $\gamma$ -amino alcohol **98** has also exhibited analgesic activity.<sup>139</sup>



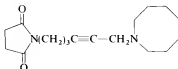
(98)

(99) A = 2-pyridyl  
R¹ = R² = H

A number of heptamethyleniminoalkyl- and arylamides show sedative activity.<sup>140,141</sup> Antispasmodic activity of 2-(1-perhydroazocinyl)-4,5-diphenyl-1,3-dioxolane has been suggested by Blicke and Millson.<sup>142</sup> Compounds of type **99** have shown local anesthetic as well as hypertensive and antipyretic activities.<sup>143</sup> Antihistaminic activity has been reported for substituted phenothiazines **100** and the dibenzazepine **101**.<sup>144</sup> The *N*-substituted acetylenic succinimide **102** is useful against Parkinson's disease.<sup>145</sup>

(100) X = Cl, H, OMe  
R = H, Me

(101)



(102)

<sup>137</sup> British Patent 1,175,639 (1970) [CA 72, 66833 (1970)].

<sup>138</sup> South African Patent 6,175 (1968) [CA 72, 12574 (1970)].

<sup>139</sup> H. A. Luts and W. L. Nobles, *J. Pharm. Sci.* **54**, 67 (1965).

<sup>140</sup> U.S. Patent 3,185,678 (1965) [CA 63, 4262 (1965)].

<sup>141</sup> W. A. Skinner, J. Kennedy, J. I. DeGraw, and H. Johnson, *J. Med. Chem.* **12**, 715 (1969).

<sup>142</sup> F. F. Blicke and H. E. Millson, Jr., *J. Am. Chem. Soc.* **77**, 32 (1955).

<sup>143</sup> British Patent 1,068,698 (1968) [CA 68, 21858 (1968)].

<sup>144</sup> French Patent M2,523 (1965) [CA 63, 2982 (1965)].

<sup>145</sup> German Patent 2,058,935 (1971) [CA 75, 63650 (1971)].

A number of investigators have reported on the autonomic nervous system activity of substituted azocines.<sup>146-153</sup> The heptamethyleneimino ring, when incorporated into an *N*-arylsulfonylsemicarbazide, enhances the antidiabetic activity of these compounds.<sup>154</sup>

1-Azacyclooct-1-yl derivatives of rifamycins have been prepared as potential antibiotics.<sup>155</sup> Dithiocarbamic acid esters of the type  $R^1R^2NCS_2CH_2$ ,  $NR^3R^4$  where  $NR^1R^2 = NR^3R^4 =$  heptamethyleneimino have exhibited activity against bacteria, fungi, and coccidia.<sup>156</sup> The incorporation of the azocine ring into penicillanic acid enhances antibacterial activity.<sup>157</sup> A number of urea<sup>158</sup> and nitrosourea<sup>159</sup> derivatives containing the azacyclooctyl ring have been suggested as neoplasm inhibitors. Azocinylguanidines show inhibition of ADP-induced platelet aggregation.<sup>160</sup> Many investigators have reported on the cardiovascular activity of azocinyl derivatives.<sup>161-189</sup>

<sup>146</sup> German Patent 1,805,029 (1969) [CA 71, 81204 (1969)].

<sup>147</sup> P. A. J. Janssen, P. J. A. Demoen, A. H. Jageneau, and J. L. M. Loomans, *J. Med. Pharm. Chem.* 1, 187 (1959).

<sup>148</sup> Z. Votava, *J. Physiol. (Paris)* 49, 417 (1957).

<sup>149</sup> U.S. Patent 2,735,847 (1956) [CA 50, 15602 (1956)].

<sup>150</sup> U.S. Patent 2,708,194 (1956) [CA 50, 5780 (1956)].

<sup>151</sup> J. P. Long and A. M. Lands, *J. Pharmacol. Exp. Ther.* 120, 46 (1957).

<sup>152</sup> U.S. Patent 2,922,795 (1960) [CA 54, 19454 (1960)].

<sup>153</sup> Hungarian Patent 398 (1971) [CA 74, 53570 (1971)].

<sup>154</sup> J. B. Wright and R. W. Willette, *J. Med. Pharm. Chem.* 5, 815 (1962).

<sup>155</sup> German Patent 2,039,320 (1974) [CA 75, 35694 (1974)].

<sup>156</sup> U.S. Patent 3,449,360 (1969) [CA 71, 49762 (1969)].

<sup>157</sup> German Patent 2,055,531 (1971) [CA 75, 49070 (1971)].

<sup>158</sup> German Patent 2,351,724 (1974) [CA 81, 25575 (1974)].

<sup>159</sup> German Patent 2,230,003 (1973) [CA 78, 97512 (1973)].

<sup>160</sup> Z. Jerushalmy, L. Skoza, M. B. Zucker, and R. Grant, *Biochem. Pharmacol.* 15, 1791 (1966).

<sup>161</sup> Belgian Patent 611,653 (1962) [CA 57, 16414 (1962)].

<sup>162</sup> R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.* 25, 1953 (1960).

<sup>163</sup> U.S. Patent 3,458,500 (1969) [CA 71, 2223 (1969)].

<sup>164</sup> W. Chen and K. Ting, *Yao Hsueh Hsueh Pao* 10, 105 (1963).

<sup>165</sup> Belgian Patent 612,665 (1963) [CA 58, 1443 (1963)].

<sup>166</sup> U.S. Patent 3,055,882 (1963) [CA 58, 9038 (1963)].

<sup>167</sup> German Patent 1,131,687 (1962) [CA 57, 11627 (1962)].

<sup>168</sup> U.S. Patent 3,006,913 (1961) [CA 56, 5940 (1961)].

<sup>169</sup> U.S. Patent 3,852,269 (1975) [CA 82, 125297 (1975)].

<sup>170</sup> U.S. Patent 3,189,600 (1965) [CA 63, 8330 (1965)].

<sup>171</sup> L. Toldy, J. Borsy, I. Toth, and M. Fekete, *Acta Chim. Acad. Sci. Hung* 43, 253 (1963).

<sup>172</sup> R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Pharm. Chem.* 5, 651 (1962).

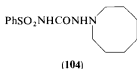
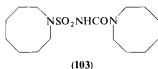
<sup>173</sup> G. C. Wright, R. P. Halliday, and C. S. Davis, *J. Pharm. Sci.* 59 (1), 105 (1970).

<sup>174</sup> German Patent 1,947,600 (1970) [CA 72, 132295 (1970)].

<sup>175</sup> Swiss Patent 346,879 (1961) [CA 56, 27383 (1961)].

<sup>176</sup> Swiss Patent 342,957 (1960) [CA 55, 2707 (1960)].

The diuretic activity of substituted azocines is well documented in the literature.<sup>190-196</sup> *N*-Nitrosoheptamethylenimine causes a high incidence of squamous carcinomas in the lung and esophagus of the rat<sup>197</sup> and hamster.<sup>198</sup> Azocinylsulfamylurea **103**<sup>199</sup> and the semicarbazide **104**<sup>200</sup> possess hypoglycemic activity.



## 2. Other Uses

Azocine derivatives have been employed as antiparasitics,<sup>201</sup> herbicides,<sup>202-209</sup> insecticides,<sup>210,211</sup> pesticides,<sup>212</sup> marine antifoulants,<sup>213,214</sup> corrosion inhibitors,<sup>215-217</sup> vulcanization accelerators,<sup>218-220</sup> dyes,<sup>221,222</sup> polymer stabilizers and inhibitors,<sup>223-225</sup> bacteriocides,<sup>226</sup> and as complexing agents in the determination of metals.<sup>227-229</sup>

- <sup>177</sup> H. Iwata, I. Yamamoto, K. Kariya, T. Tetsuo, N. Takayanagi, and D. Marishita, *Oyo Yakuri* **14**, 235 (1977).
- <sup>178</sup> M. S. Forrester, *Diss. Abstr. Int. B* **35**, 3258 (1978).
- <sup>179</sup> L. D. Wise, G. C. Morrison, and K. Egan, *J. Med. Chem.* **17**, 1232 (1974).
- <sup>180</sup> Hungarian Patent 155,990 (1969) [*CA* **71**, 91345 (1969)].
- <sup>181</sup> U.S. Patent 2,897,195 (1959) [*CA* **54**, 1576 (1959)].
- <sup>182</sup> C. Cheng and J. Chi, *Yao Hsueh Hsueh Pao* **10**, 655 (1963).
- <sup>183</sup> R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.* **80**, 3769 (1958).
- <sup>184</sup> T. Pai and J. Chi, *Yao Hsueh Hsueh Pao* **30**, 146 (1964).
- <sup>185</sup> T. Pai and J. Chi, *Yao Hsueh Hsueh Pao* **29**, 28 (1963).
- <sup>186</sup> V. Marigliano, V. Musca, C. Cordova, and I. Cammarella, *Boll. Soc. Ital. Biol. Sper.* **52**, 1131 (1976).
- <sup>187</sup> South African Patent 5,504 (1969) [*CA* **72**, 120666 (1970)].
- <sup>188</sup> U.S. Patent 4,001,214 (1977) [*CA* **87**, 39315 (1977)].
- <sup>189</sup> German Patent 2,314,187 (1975) [*CA* **80**, 27124 (1975)].
- <sup>190</sup> J. B. Bicking, J. M. Mason, O. W. Wottersdorf, Jr., J. H. Jones, S. F. Kwong, C. M. Robb, and E. J. Cragoe, Jr., *J. Med. Chem.* **8**, 638 (1965).
- <sup>191</sup> British Patent 914,613 (1963) [*CA* **59**, 7492 (1963)].
- <sup>192</sup> E. Jucker, A. Lindenmann, E. Schenker, E. Flueckiger, and M. Tieschler, *Arzneim.-Forsch.* **13**, 269 (1963).
- <sup>193</sup> E. Jucker and A. Lindenmann, *Helv. Chim. Acta* **45**, 2316 (1962).
- <sup>194</sup> Netherlands Patent 6,414,604 (1966) [*CA* **64**, 3504 (1966)].
- <sup>195</sup> Belgian Patent 662,507 (1967) [*CA* **66**, 10961 (1967)].
- <sup>196</sup> Japanese Patent 9,253 (1971) [*CA* **75**, 31644 (1971)].
- <sup>197</sup> W. Lijinsky, L. Tomatis, and C. E. M. Wenyon, *Proc. Soc. Exp. Biol. Med.* **130** (3), 945 (1969).

### III. Benzazocines

#### A. PREPARATIVE METHODS

##### 1. Via Ring Closure

The first preparation of a benzazocine (**105**; R = SO<sub>2</sub>Ph) was carried out by Braun and Bayer via the cyclization of ethyl *N*-benzenesulfonyl-*N*-(4-phenylbutyl)amino acetate.<sup>230</sup> Numerous methods for the synthesis of benzazocines utilizing aromatic electrophilic substitution have been reported. For example, **106** was prepared by cyclization of the appropriate

<sup>198</sup> W. Lijinsky, A. Ferrero, R. Montesano, and E. M. Charles, *Z. Krebsforsch.* **74** (2), 185 (1970).

<sup>199</sup> J. W. McFarland, C. F. Gerber, and W. M. McLamore, *J. Med. Chem.* **8**, 781 (1965).

<sup>200</sup> French Patents 1,332,375; 1,335,993 (1964) [*CA* **60**, 614 (1964); *CA* **60**, 1720 (1964)].

<sup>201</sup> German Patent 2,056,606 (1971) [*CA* **75**, 63183 (1971)].

<sup>202</sup> German Patent 1,964,441 (1970) [*CA* **73**, 120676 (1970)].

<sup>203</sup> U.S. Patent 3,766,172 (1974) [*CA* **80**, 37022 (1974)].

<sup>204</sup> German Patent 2,219,923 (1974) [*CA* **80**, 27127 (1974)].

<sup>205</sup> British Patent 1,136,679 (1969) [*CA* **70**, 68420 (1969)].

<sup>206</sup> U.S. Patent 3,357,815 (1968) [*CA* **68**, 105034 (1968)].

<sup>207</sup> U.S. Patent 3,330,822 (1967) [*CA* **67**, 108568 (1967)].

<sup>208</sup> British Patent 1,167,084 (1970) [*CA* **72**, 12603 (1970)].

<sup>209</sup> U.S. Patent 3,303,014 (1967) [*CA* **67**, 43674 (1967)].

<sup>210</sup> German Patent 1,812,497 (1979) [*CA* **71**, 12425 (1969)].

<sup>211</sup> German Patent 2,029,753 (1971) [*CA* **74**, 53792 (1971)].

<sup>212</sup> South African Patent 6,326 (1968) [*CA* **72**, 43234 (1970)].

<sup>213</sup> U.S. Patent 3,391,172 (1968) [*CA* **69**, 58873 (1968)].

<sup>214</sup> U.S. Patent 3,281,453 (1967) [*CA* **66**, 10661 (1967)].

<sup>215</sup> U.S. Patent 3,091,591 (1963) [*CA* **59**, 2459 (1963)].

<sup>216</sup> N. Hackerman, R. M. Hurd, and R. R. Annand, *Corrosion* **18**, 371 (1962).

<sup>217</sup> H. F. Finley and N. Hackerman, *J. Electrochem. Soc.* **107**, 259 (1960).

<sup>218</sup> U.S. Patent 3,468,876 (1961) [*CA* **71**, 112835 (1969)].

<sup>219</sup> U.S. Patent 3,422,078 (1961) [*CA* **71**, 58783 (1967)].

<sup>220</sup> J. J. D'Amico, E. Morita, and E. J. Young, *Rubber Chem. Technol.* **41**, 704 (1968).

<sup>221</sup> British Patent 795,134 (1959) [*CA* **54**, 3722 (1959)].

<sup>222</sup> Belgian Patent 625,538 (1962) [*CA* **57**, 15413 (1962)].

<sup>223</sup> Japanese Patent 18,096 (1967) [*CA* **66**, 28685 (1967)].

<sup>224</sup> French Patent 1,372,838 (1965) [*CA* **62**, 2781 (1965)].

<sup>225</sup> U.S. Patent 2,748,113 (1956) [*CA* **51**, 8815 (1956)].

<sup>226</sup> U.S. Patent 3,320,328 (1968) [*CA* **68**, 95714 (1968)].

<sup>227</sup> H. Sibarska-Tomicka, *Microchem. J.* **16**, 437 (1971).

<sup>228</sup> H. Sibarska-Tomicka, *Chem. Anal. (Warsaw)* **15**, 947 (1970).

<sup>229</sup> H. Sibarska-Tomicka, *Chem. Anal. (Warsaw)* **14**, 97 (1969).

<sup>230</sup> J. V. Braun and O. Bayer, *Ber. Dtsch. Chem. Ges. B* **60**, 1257 (1927).

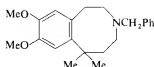




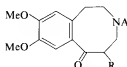
- (105) R = SO<sub>2</sub>Ph  
 R = CH<sub>2</sub>CH<sub>2</sub>OH  
 R = Me



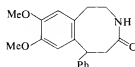
(106)



(107)



(108) A = C(OMe)<sub>2</sub>, SO<sub>2</sub>Ph  
 R = H, Me



(109)

diphenylcarbinol.<sup>231</sup> In a similar manner, a large number of other benzazocines have been prepared.<sup>232</sup> *N*-Benzyl-*N*-dimethylallyl-3,4-dimethoxyphenethylamine was ring closed with 80% H<sub>2</sub>SO<sub>4</sub> to give the benzazocine **107**.<sup>233</sup> Comer and co-workers<sup>234</sup> synthesized a number of tetrahydro-3-benzazocinones (**108**) by treating the appropriate acids with polyphosphoric acid. Lactam **109** was prepared by treating the properly substituted cinnamamide with phosphoric acid.<sup>235</sup> A number of these ring closures have been accomplished under Friedel-Crafts conditions utilizing different substrates, i.e., haloamines,<sup>236</sup> aminobutanols or aminobutenes,<sup>237</sup> and acid chlorides.<sup>238,239</sup>

Pecherer and co-workers have prepared a number of benzazocinones by heating the substituted 3-phenylpropionic acids **110**<sup>240</sup> or the substituted phenylacetic acid **111**.<sup>241</sup> Huisgen and co-workers<sup>242</sup> have published a

<sup>231</sup> V. S. Shklyayev and Yu. S. Cherkryshkim, *Zh. Org. Khim.* **4**, 1046 (1968).

<sup>232</sup> Japanese Patent 43,545 (1971) [*CA* **76**, 59486 (1972)].

<sup>233</sup> Japanese Patent 08,827 (1972) [*CA* **77**, 5382 (1972)].

<sup>234</sup> W. T. Comer, J. D. Catt, W. Lesley, C. M. Combs, and S. J. Dykstra, *J. Heterocycl. Chem.* **10**, 519 (1973).

<sup>235</sup> R. E. Harmon, B. L. Jensen, S. K. Gupta, and J. D. Nelson, *J. Org. Chem.* **35**, 825 (1970).

<sup>236</sup> L. W. Deady, N. H. Pirzada, and R. D. Topsom, *J. C. S. Perkin I*, No. 8, 782 (1973).

<sup>237</sup> Y. Sawa, T. Kato, A. Moutomoto, M. Toru, M. Hou, and H. Fujimura, *Yakugaku Zasshi* **95**, 251 (1975).

<sup>238</sup> U.S. Patent 3,442,890 (1969) [*CA* **71**, 61249 (1969)].

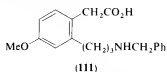
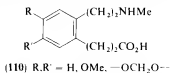
<sup>239</sup> J. Schlademan and R. Partch, *J. C. S. Perkin I* (2), 213 (1972).

<sup>240</sup> B. Pecherer, J. Stumpf, and A. Brossi, *Helv. Chim. Acta* **53**, 763 (1970).

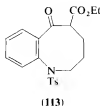
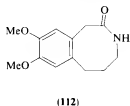
<sup>241</sup> B. Pecherer, F. Humiec, and A. Brossi, *Helv. Chim. Acta* **54**, 743 (1971).

<sup>242</sup> R. Huisgen, H. Konig, and N. Blecker, *Chem. Ber.* **92**, 429 (1959).

direct preparation of a 1-benzazocine from *o*- and *m*-halo derivatives of 5-phenyl-*N*-methylpentylamine via a benzyne intermediate.

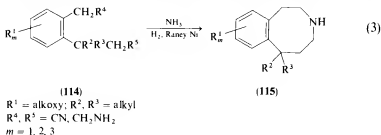


Benzazocines have also been synthesized using photolytic methods.<sup>243-245</sup> For example, **112** was prepared by photochemical cyclization of *N*-(chloroacetyl)-3-(3,4-dimethoxyphenyl)propylamine.<sup>243</sup>



Base-Catalyzed cyclization of diesters provide another synthetic route. For example, a Dieckmann condensation is used to prepare the benzazocinone **113**.<sup>246</sup> A large number of hexahydro-1-benzazocin-5-ones were made in a similar manner.<sup>247</sup> Belleau<sup>248</sup> obtained the 2-benzazocine **105** ( $R = CH_2CH_2OH$ ) from the condensation of ethanolamine with the appropriate dihalide.

A number of investigators have utilized reductive ring closures as a means of making benzazocines. For example, 3-benzazocines **115** were prepared by



<sup>243</sup> O. Yonemitsu, Y. Okuno, and K. Hemmu, *J. Chem. Soc. D* (14), 745 (1971).

<sup>244</sup> H. H. Ong and E. L. May, *J. Org. Chem.* **38**, 924 (1973).

<sup>245</sup> Y. Sawa, T. Kato, T. Masuda, M. Hori, and H. Fujimura, *Yakugaki Zasshi* **95**, 261 (1975).

<sup>246</sup> G. R. Proctor and W. I. Ross, *J. C. S. Perkin I* (6), 885 (1972).

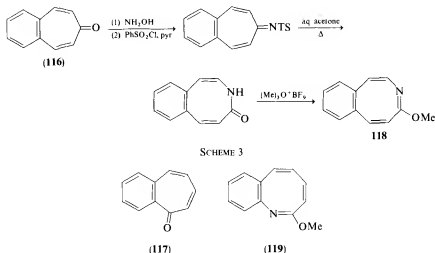
<sup>247</sup> Japanese Patent 88,984 (1976) [*CA* **86**, 121195 (1977)].

<sup>248</sup> B. Belleau, *J. Med. Pharm. Chem.* **1**, 327 (1959).

cyclization of the appropriately substituted *o*-ethyltoluenes **114** (Eq. 3).<sup>249,250</sup>

## 2. Via Ring Expansion

The most common method of preparing the benzazocine ring system by ring expansion utilizes the Beckmann rearrangement on a benzuberone oxime<sup>251-254</sup> or benztropone oxime<sup>255</sup> and the Schmidt rearrangement on the ketone.<sup>256-259</sup> Paquette and co-workers have used the rearrangement of benztropones **116** and **117** as a way of preparing the completely unsaturated benzazocines **118** and **119**, respectively. This is exemplified by Scheme 3.<sup>260</sup>



SCHEME 3

<sup>249</sup> Y. Sawa, Y. Kawakami, T. Hattori, T. Masuda, M. Hori, and H. Fujimwia, *Chem. Pharm. Bull.* **23**, 2211 (1975).

<sup>250</sup> Japanese Patent 11,919 (1975) [*CA* **83**, 206130 (1975)].

<sup>251</sup> R. T. Conley and L. J. Frainier, *J. Org. Chem.* **27**, 3844 (1962).

<sup>252</sup> J. Humbert and A. Laurent, *C. R. Hebd. Seances Acad. Sci., Ser. C* **272**, 1165 (1971).

<sup>253</sup> D. H. Jones, G. F. Stephenson, G. W. Spray, and W. R. Wragg, *J. Chem. Soc. C* **16**, 2176 (1969).

<sup>254</sup> Netherland Patent 6,516,320 (1966) [*CA* **64**, 15354 (1966)].

<sup>255</sup> R. M. Coates and E. F. Johnson, *J. Am. Chem. Soc.* **93**, 4016 (1971).

<sup>256</sup> H. J. Havera, J. W. VanDyke, Jr., T. M. H. Liu, and L. F. Sanciko, *J. Med. Chem.* **12**, 580 (1969).

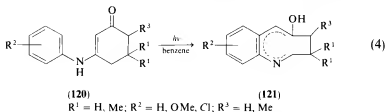
<sup>257</sup> N. J. Hjelte and T. Agback, *Acta Chem. Scand.* **18**, 191 (1964).

<sup>258</sup> P. A. S. Smith and W. L. Berg, *J. Org. Chem.* **26**, 27 (1961).

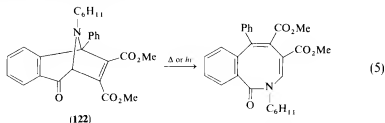
<sup>259</sup> M. Tomita, S. Minami, and S. Uyeo, *J. Chem. Soc. C* (2), 183 (1969).

<sup>260</sup> L. A. Paquette, L. B. Anderson, J. F. Hansen, S. A. Lang, Jr., and H. Berk, *J. Am. Chem. Soc.* **94**, 4907 (1972).

The photochemical ring expansion of the enamino ketones **120** also gives rise to benzazocinones **121** (Eq. 4).<sup>261,262</sup> Padwa and co-workers<sup>263,264</sup>



have obtained benzazocines from the thermal or photochemical rearrangement of the aziridine cycloadducts **122** (e.g., Eq. 5).



A number of methods have been reported for the preparation of benzazocinediones which utilize an oxidative ring opening of 2,3-cyclopentenoindoles **123**.<sup>265-268</sup> Acid-Catalyzed ring opening of the fused azetidine system **124** also affords a benzazocine (**125**,  $R^1 = R^2 = H$ ,  $R^3 = OMe$ ).<sup>269</sup> Ring expansion of 1-phenyl-1-vinyl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines affords 3-benzazocines such as **125** ( $R^1 = Me$ ,  $R^2 = Ph$ ,  $R^3 = H$ ).<sup>270</sup>



<sup>261</sup> K. Yamada, T. Konakahara, S. Ishihara, H. Kanamori, T. Itoh, K. Kimura, and H. Iida, *Tetrahedron Lett.* (25), 2513 (1972).

<sup>262</sup> K. Yamada, M. Kamei, Y. Nakano, H. Iida, *Chiba Daigaku Kogakubu Kenkyu Hokoku* **25** (48), 73 (1974).

<sup>263</sup> A. Padwa, P. Sackman, E. Shefter, and E. Vega, *J. C. S. Chem. Commun.* (11), 680 (1972).

<sup>264</sup> A. Padwa and E. Vega, *J. Org. Chem.* **40**, 175 (1975).

<sup>265</sup> Japanese Patent 39,345 (1971) [*CA* **76**, 25117 (1972)].

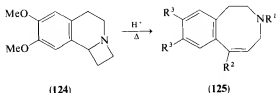
<sup>266</sup> B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.* **73**, 2641 (1951).

<sup>267</sup> G. Jones and G. T. Tringham, *J. C. S. Perkin. I* (13), 1280 (1975).

<sup>268</sup> German Patent 2,438,413 (1975) [*CA* **83**, 43364 (1975)].

<sup>269</sup> J. Kobor, *Szegedi Pedagóg. Forskola Ekv., Masodik Resz.*, **41** (1967).

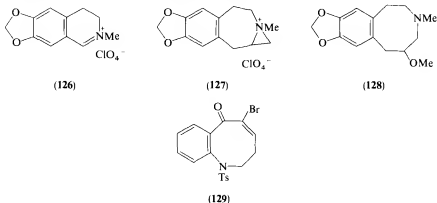
<sup>270</sup> H. W. Bersch, D. Hoff, and D. Schon, *Arch. Pharm. (Weinheim, Ger.)* **311** (12), 1029 (1978).



Another route to a benzazocine, e.g., **105** ( $R = \text{Me}$ ), is via the base-catalyzed ring expansion of a 1,1-dimethyl-2-phenylpiperidinium salt.<sup>271</sup>

### 3. Via Addition to a Heterocycle

Treatment of 2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium perchlorate (**126**) with diazomethane afforded a mixture of aziridinium salts including **127**. This underwent reaction with methanol to produce the 3-benzazocine **128**.<sup>272</sup> The 2-benzazocine **129** is obtained in a similar fashion by addition of dibromocarbene to a benzazepine.<sup>273</sup>



A number of investigators have synthesized benzazocine derivatives by treating reduced quinolines and isoquinolines with dimethylacetylene dicarboxylate (DMA) or with other acetylenes (Eqs. 6–9).<sup>274–277</sup>

<sup>271</sup> G. C. Jones and C. R. Hauser, *J. Org. Chem.* **27**, 3572 (1962).

<sup>272</sup> H. O. Bernhard and V. Snieckus, *Tetrahedron* **27** (11), 2091 (1971).

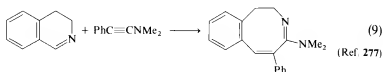
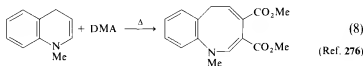
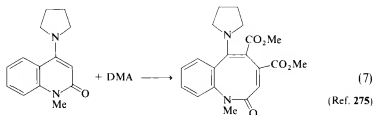
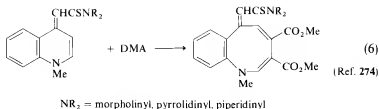
<sup>273</sup> W. I. Ross and G. R. Proctor, *J. C. S. Perkin I* (6), 889 (1972).

<sup>274</sup> G. Kobayashi, Y. Matsuda, Y. Tominaga, and K. Mizuyama, *Chem. Pharm. Bull.* **23** (11), 2749 (1975).

<sup>275</sup> D. J. Haywood and S. T. Reid, *J. C. S. Perkin I* (22) 2457 (1977).

<sup>276</sup> P. G. Lehman, *Tetrahedron Lett.* (48), 4863 (1972).

<sup>277</sup> R. Fuks and H. G. Viehe, *Chem. Ber.* **103**, 573 (1970).



#### 4. Benzazocines as Mitomycin Precursors

Formation of 1-benzazocines and their subsequent ring closure are key reactions in the synthesis of the mitomycins and related compounds (see Section III.D). Ring opening of pyrroloindoles **130** with cyanogen bromide afforded **131**.<sup>278,279</sup> Opening of **130** with ethyl chloroacetate or acetic anhydride gave **132**.<sup>280</sup> The Dieckmann condensation gives 1-benzazocine-5-ones.<sup>281,282</sup> Intramolecular Michael reactions were used to prepare

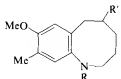
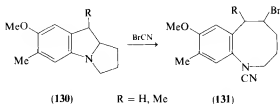
<sup>278</sup> T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *J. C. S. Perkin I* (6), 662 (1978).

<sup>279</sup> T. Kametani, K. Takahashi, I. Masataka, and K. Fukumoto, *Heterocycles* **6**, 1371 (1977).

<sup>280</sup> T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles* **9**, 435 (1978).

<sup>281</sup> J. W. Lown and T. Itoh, *Can. J. Chem.* **53**, 960 (1975).

<sup>282</sup> T. Itoh, T. Hata, and J. W. Lown, *Heterocycles* **4**, 47 (1976).



1-benzazocines which could then be ring closed.<sup>283-284</sup> For example, **133** reacts to give **134**, a precursor to the mitomycins (see Section III,D).



## B. THEORETICAL ASPECTS

Benzannulation results in an attenuation of aromaticity effects in  $4n + 2\pi$ -systems.<sup>255</sup> The base-catalyzed hydrogen isotope exchange and isomerization reactions of isomeric dihydrobenzazocines **135** and **136** show these compounds have moderately enhanced kinetic acidity as compared with dihydroquinoline models and is attributable to a small degree of aromatic stabilization in the incipient  $10\pi$  electron benzazocinyl anions.<sup>255</sup>

The isomers **137** and **138** differed in their behavior on electrochemical reduction.<sup>260</sup> Both compounds add one electron to give radical anions,

<sup>283</sup> F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, *J. Am. Chem. Soc.* **99**, 4835 (1977).

<sup>283a</sup> F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, *J. Am. Chem. Soc.* **99**, 8115 (1977).

<sup>284</sup> T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, and Y. Kishi, *Tetrahedron Lett.*, 4295 (1977).

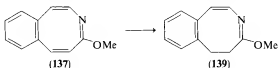


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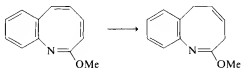
(136)

paralleling the behavior of the carbocyclic analog. However, whereas **137** is reduced to the radical anion which then decomposes rapidly to one or more electroinactive products, **138** is reduced to its highly stable and aromatic dianion in a manner similar to substituted azocines. The alkali metal reduction of **137** and **138** parallels the behavior of the nonbenzo parent, giving **139** and **140**, respectively, after protonation of the intermediate dianions. Neither benzazocine produces the anion as easily as does methoxyazocine. This annelation effect was attributed either to the electronic effect of the benzene ring or to increased steric hindrance to ring flattening.



(137)

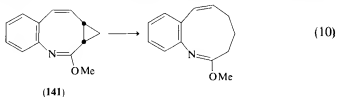
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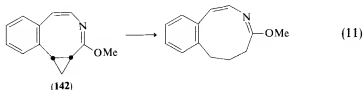
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The benzhomazocines **141** and **142** behave similarly to the homozocines in that the integrity of the imino ether is maintained and the cyclopropane ring is opened (Eqs. 10 and 11).<sup>71</sup> However, in **143** and **144**, disrotatory



(141)

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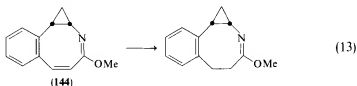
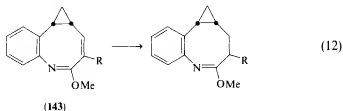


(142)

(11)



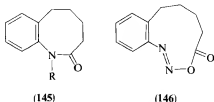
cyclopropane opening would have to destroy temporarily the benzene rings, and with these compounds, simple double bond reduction occurs, the cyclopropane ring surviving potassium in ammonia (Eqs. 12 and 13). The regioselectivity of reduction was further explained by assuming that an electron



goes preferentially to the carbon adjacent to the imino carbon, the imino system being able to stabilize the anion. This explains why simple double bond reduction does not occur in **141** and **142** since the  $\text{N}=\text{C}(\text{OCH}_3)\text{C}^-$  system could only be formed here by cyclopropane scission.

### C. STEREOCHEMISTRY

The properties of benzazocines are best explained by a nonplanar tul conformation, similar to azocine.<sup>68</sup> The *N*-nitrosobenzosuberone isoxime **145** ( $\text{R} = \text{NO}$ ) underwent rearrangement to the diazoester **146** much faster than small ring benzolactams, paralleling the behavior of the nonbenzo analog **62** (see Section II.C).<sup>285</sup> In contrast to **62**, **145** ( $\text{R} = \text{NO}$ ) reacted even faster than its nine-membered homolog. This is attributed to the inability of the benzene ring to conjugate well with the developing azo group in the transition state.



<sup>285</sup> R. Huisgen and L. Krause, *Justus Liebigs Ann. Chem.* **574**, 171 (1951).

Lactam **145** ( $R = H$ ) exists in the cis form, the Ar—N resonance being less significant than the amide ( $N-C=O$ ) resonance.<sup>286</sup>

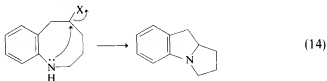
## D. REACTIONS

### 1. Eight-Membered Ring Preserved

Those reactions involving substitution at nitrogen include reactions with alkyl halides<sup>286–292</sup> and acylations.<sup>288,293–297</sup> In addition, a ketolactam was arylated with a phenyl Grignard.<sup>298</sup>

### 2. Ring Contraction: Synthesis of the Mitomycins

The mitomycins (**147**) are a family of compounds that possess both anti-biotic and antitumor activity. As noted earlier (Section III,A) ring closure of 1-benzazocines affords a route to mitomycins (**147**) and related compounds (Eq. 14).<sup>299,300</sup> Compound **132** was ring closed in this manner.<sup>278,279</sup> The 1-



<sup>286</sup> R. Huisgen, I. Ugi, H. Brode, and E. Rauenbusch, *Justus Liebigs Ann. Chem.* **586**, 30 (1954) [*CA* **49**, 10881 (1955)].

<sup>287</sup> Netherland Patent 6,514,240 (1966) [*CA* **65**, 12181 (1966)].

<sup>288</sup> German Patent 1,906,000 (1969) [*CA* **72**, 12600 (1970)].

<sup>289</sup> U.S. Patent 3,475,416 (1969) [*CA* **72**, 3400 (1970)].

<sup>290</sup> British Patent 1,305,278 (1973) [*CA* **78**, 124462 (1973)].

<sup>291</sup> U.S. Patent 3,840,522 (1974) [*CA* **82**, 31277 (1975)].

<sup>292</sup> Czech Patent 170,665 (1977) [*CA* **88**, 169997 (1978)].

<sup>293</sup> French Patent 1,542,160 (1968) [*CA* **71**, 124525 (1969)].

<sup>294</sup> U.S. Patent 3,748,321 (1973) [*CA* **79**, 92303 (1973)].

<sup>295</sup> British Patent 1,334,684 (1973) [*CA* **80**, 47868 (1974)]; Japanese Patent 11,394 (1975) [*CA* **83**, 206131 (1975)].

<sup>296</sup> Japanese Patent 34,992 (1974) [*CA* **84**, 43884 (1976)].

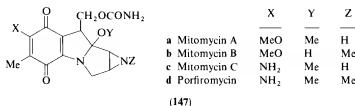
<sup>297</sup> Japanese Patent 2,516 (1975) [*CA* **83**, 114248 (1975)].

<sup>298</sup> Japanese Patent 41,200 (1974) [*CA* **82**, 156135 (1975)].

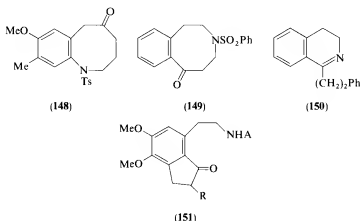
<sup>299</sup> For a review of this subject, see T. Kametani and K. Tokahashi, *Heterocycles* **9**, 293 (1978), and references cited therein.

<sup>300</sup> M. Ihara, K. Takahashi, Y. Kigawa, T. Ohswa, K. Fukumoto, and T. Kametani, *Symp. Heterocycl. [Pap.]*, 160 (1977); *Heterocycles* **6**, 1658 (1977) [*CA* **88**, 66280 (1978)].

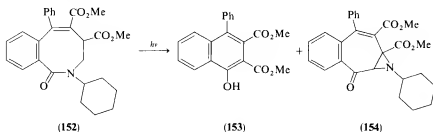
benzazocine-5-one (**148**) prepared by Dieckmann reaction, underwent similar closure.<sup>281,282</sup> The actual synthesis of mitomycin A (**147a**),<sup>284</sup> mitomycin C (**147c**),<sup>284</sup> and porfiromycin (**147d**)<sup>283a</sup> was achieved by ring closure of **134**.

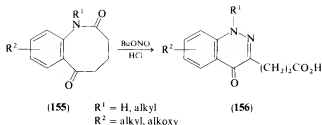


Several 3-benzenesulfonyl- and 3-benzoyl-2,3,4,5-tetrahydro-3-benzazocine-6(1*H*)-ones were found to undergo acid-catalyzed ring contraction.<sup>234</sup> For example, **149** on treatment with HBr and phenol yielded **150**, whereas



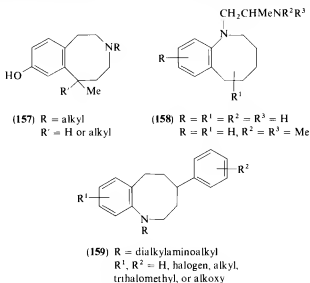
compound **108** with polyphosphoric acid gave **151**. Other benzazocine ring contractions are the photochemical reaction of lactam **152** to give **153** and **154**<sup>263</sup> and the conversion of various substituted benzazocines **155** to pharmacologically useful cinnolines **156**.<sup>268</sup>





## E. APPLICATIONS

A variety of benzazocines possess biological activity. For example, a number of substituted benzazocines exhibit analgesic and antiinflammatory activity, e.g., **157**.<sup>240,301-305</sup> Benzazocines have also been proven to affect the central nervous system<sup>306-310</sup>; e.g., compounds of the type **158** are used as antidepressants, stimulants, sedatives, and hypnotics. Derivatives of **159**



<sup>301</sup> German Patent 2,353,062 (1974) [*CA* **81**, 37487 (1974)].

<sup>302</sup> Canadian Patent 884,889, 883,829 (1970) [*CA* **76**, 14372 (1976)].

<sup>303</sup> M. E. Rogers, H. H. Ong, and E. L. May, *J. Med. Chem.* **18**, 1036 (1975).

<sup>304</sup> German Patent 2,652,568 (1977) [*CA* **87**, 102196 (1977)].

<sup>305</sup> U.S. Patent 4,107,303 (1978) [*CA* **90**, 87307 (1978)].

<sup>306</sup> Japanese Patent 39,344 (1971) [*CA* **76**, 76111 (1972)].

<sup>307</sup> Japanese Patent 45,874 (1974) [*CA* **83**, 9836 (1975)].

<sup>308</sup> German Patent 2,050,711 (1972) [*CA* **76**, 72432 (1972)].

<sup>309</sup> Japanese Patent 1,276 (1975) [*CA* **83**, 43213 (1975)].

<sup>310</sup> German Patent 1,909,038 (1970) [*CA* **72**, 43755 (1970)].

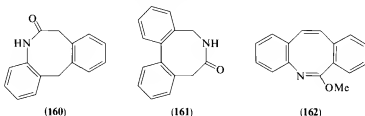
show hypotensive activity.<sup>311</sup> Diuretic activity has been reported for 6-(*p*-chlorophenyl)-8,9-dimethoxy-1,2,3,4-tetrahydro-1-benzazocines.<sup>312</sup>

## IV. Dibenzazocines

### A. PREPARATIVE METHODS

#### 1. *Via Ring Expansion*

The major ring expansion route to the dibenzazocines is via a Beckmann or Beckmann-type rearrangement of the oxime. Lactams **160**<sup>313</sup> and **161**<sup>314</sup> were prepared by ring expansion of the corresponding dibenzosuberones. Other dibenz[*b,f*]azocines have been similarly made.<sup>315–320</sup> The fully unsaturated dibenzazocine **162** has also been prepared from the corresponding lactam in a manner similar to that used for **118** (Scheme 3).<sup>260</sup>



Treatment of aziridine **163** with HCl affords the chloride **164** in high yield.<sup>321</sup> Dibenzazocines have also been prepared by oxidative ring opening of indenoindoles using ozone<sup>322</sup> or periodic acid.<sup>323</sup> Dibenzazabicyclo compound **165** can be converted to dibenzazocines **166** and **167** via Hoff-

<sup>311</sup> U.S. Patent 3,330,823 (1968) [*CA* **68**, 95713 (1968)].

<sup>312</sup> German Patent 1,933,300 (1970) [*CA* **72**, 90333 (1970)].

<sup>313</sup> Czech. Patent 120,195 (1968) [*CA* **68**, 78162 (1968); **69**, 96512 (1968)].

<sup>314</sup> Japanese Patent 2625 (1966) [*CA* **64**, 14175 (1966)].

<sup>315</sup> M. Miloshev and B. Aleksiev, *Monatsh. Chem.* **102** (1), 88 (1971).

<sup>316</sup> F. Sowinski and H. L. Yale, *Arzneim.-Forsch.* **5**, 117 (1964).

<sup>317</sup> C. van der Stelt, W. J. Heus, and W. T. Hauta, *Arzneim.-Forsch.* **5**, 116 (1964).

<sup>318</sup> U.S. Patent 3,448,102 (1969) [*CA* **71**, 49802 (1969)].

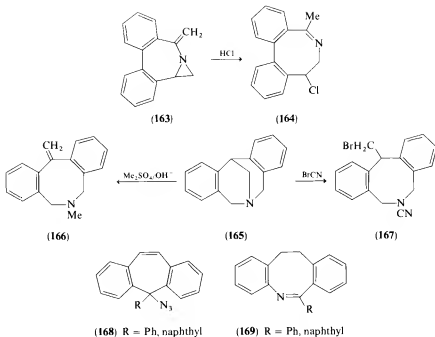
<sup>319</sup> G. A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.* **6**, 255 (1963).

<sup>320</sup> W. J. van Der Burg, I. L. Bonta, J. Delobelle, C. Ramon, and B. Vargatti, *J. Med. Chem.* **13** (1), 35 (1970).

<sup>321</sup> A. Padwa, A. Ku, H. Ku, and A. Mazzu, *Tetrahedron Lett.* (6), 551 (1977).

<sup>322</sup> German Patent 1,952,019 (1970) [*CA* **73**, 45556 (1970)].

<sup>323</sup> L. Dolby and P. D. Lord, *J. Org. Chem.* **34**, 2988 (1969).



mann<sup>324,325</sup> and von Braun degradations.<sup>325</sup> Looker photolyzed azide **168** and obtained the dibenz[*b,f*]azocine **169** as a minor product.<sup>326</sup>

## 2. Via Ring Closure

Thermolysis of 1,3-bis(*o*-aminophenyl)propane yields the dibenz[*b,g*]-azocine **170** (X = NH, Y = CH<sub>2</sub>).<sup>327,328</sup> In a similar fashion, 2,2'-bisamino-methyldiphenylmethane provides the dibenz[*c,f*]azocine **170** (X = CH<sub>2</sub>, Y = NH).<sup>329</sup> This latter ring system has also been prepared by treating a dihalide with ammonia,<sup>246</sup> a substituted amine,<sup>329,330</sup> or *t*-butyl carbazate.<sup>331</sup>

<sup>324</sup> H. Takayama, T. Nomoto, T. Suzuki, M. Takamoto, and T. Okamoto, *Heterocycles* **9**, 1545 (1978).

<sup>325</sup> H. Takayama, M. Takamoto, and T. Okamoto, *Tetrahedron Lett.* (15), 1307 (1978).

<sup>326</sup> J. J. Looker, *J. Org. Chem.* **36**, 2681 (1971).

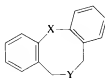
<sup>327</sup> J. C. L. Fouche, *Ind. Chim. Belge* **32** (Spec. No., Pt. III), 226 (1967).

<sup>328</sup> British Patent 926,335 (1964) [*CA* **61**, 1843 (1964)].

<sup>329</sup> G. Pala, A. Montegani, and E. Zugna, *Tetrahedron* **26** (5), 1275 (1970).

<sup>330</sup> Japanese Patent 3,628 (1966) [*CA* **64**, 19578 (1966)].

<sup>331</sup> L. A. Carpino, J. Ferrari, S. Growecka, and S. Herliczek, *J. Org. Chem.* **34**, 2009 (1969).

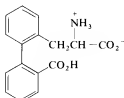


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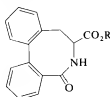
Dibenz[*c,e*]azocines **171** have been prepared by ring closure of halo-biphenyls with primary amines<sup>330,332</sup> and by photochemical cyclization of *N*-benzyl- $\beta$ -(2-halophenyl)ethylamines.<sup>332-334</sup> Similar closures have been effected by photolysis of diazonium salts,<sup>335</sup> anodic oxidation,<sup>336</sup> and trifluoromethanesulfonic acid.<sup>337</sup> Ring closure of **172** affords **173**.<sup>338</sup>



(171)

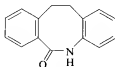


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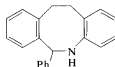


(173)

Dibenz[*b,f*]azocines **175** and **176** have been prepared by cyclization of **174** (A = NCO)<sup>339,340</sup> and **174** (A = NHCH<sub>2</sub>Ph),<sup>341</sup> respectively. Keto-imide **177** (X = NH) was obtained by treating **177** (X = O) with ammonia.<sup>342</sup>

(174) A = NCO, NHCH<sub>2</sub>Ph

(175)



(176)

<sup>332</sup> P. W. Jeffs, J. F. Hansen, and G. A. Brine, *J. Org. Chem.* **40**, 2883 (1975).

<sup>333</sup> P. W. Jeffs and J. F. Hansen, *J. Am. Chem. Soc.* **89**, 2798 (1967).

<sup>334</sup> Japanese Patent 86,486 (1976) [*CA* **86**, 106413 (1977)].

<sup>335</sup> Japanese Patent 110,586 (1976) [*CA* **86**, 155530 (1977)].

<sup>336</sup> M. Sainsbury and J. Wyatt, *J. C. S. Perkin I*, 661 (1976).

<sup>337</sup> Y. Endo, T. Ohta, K. Shudo, and T. Okamoto, *Heterocycles* **8**, 367 (1977).

<sup>338</sup> B. Belleau and R. Chevalier, *J. Am. Chem. Soc.* **90**, 6864 (1968).

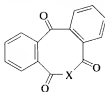
<sup>339</sup> O. Schindler, R. Blaser, and F. Hunziker, *Helv. Chim. Acta* **49**, 985 (1966).

<sup>340</sup> Netherland Patent 6,411,504 (1966) [*CA* **64**, 8223 (1966)].

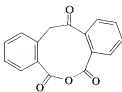
<sup>341</sup> K. Pelv, V. Seidlova, E. Svatek, M. Rajsner, and M. Protiva, *Collect. Czech. Chem. Commun.* **33** (6), 1880 (1968).

<sup>342</sup> W. Baker, J. F. W. McOmie, and H. Finkelstein, *Chem. Ber.* **92**, No. 5, xxxvii (1959).

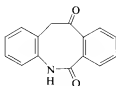
The structure of ketoanhydride **178** was supported by its conversion to ketolactam **179** via a Schmidt reaction.<sup>343</sup>



(177)



(178)



(179)

### 3. Apogalanthamines

The earliest reported synthetic approach to pharmacologically interesting apogalanthamine (**181**) was via the ring expansion of galanthamine (**180**) with aqueous HBr.<sup>344-346</sup> O-Methylapogalanthamine was obtained with HCl,<sup>345,347,348</sup> or hydrazine in base.<sup>349</sup> Another major synthetic approach to apogalanthamine derivatives is ring closure of biphenyls.<sup>339-341,343-355</sup> Kametani and co-workers<sup>356</sup> obtained **183** by treating dienol **182** or dienone **184** with a sulfuric acid/acetic anhydride mixture. Kobayashi and co-workers<sup>357-359</sup> utilized a photolytic ring closure to synthesize apogalanthamine analogs employing the method used in synthesizing **171**.

<sup>343</sup> G. Caronna and B. Ricotta, *Gazz. Chim. Ital.* **83**, 387 (1953).

<sup>344</sup> S. Kobayashi, T. Shingu, and S. Uyeo, *Chem. Ind. (London)*, 177 (1956).

<sup>345</sup> S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, 638 (1957).

<sup>346</sup> L. Bubeva-Ivanova, *Chem. Ber.* **95**, 1348 (1962).

<sup>347</sup> A. Abdusamatov, Kh. A. Abduazimov, and S. Yu. Yunusov, *Khim. Priir. Soedin.* **5** (3), 194 (1969).

<sup>348</sup> U.S.S.R. Patent 227,526 (1969) [*CA* **71**, 13253 (1969)].

<sup>349</sup> T. Kametani, *J. Chem. Soc. C* (3), 590 (1971).

<sup>350</sup> S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, 639 (1957).

<sup>351</sup> J. Kozumi, S. Kobayashi, and S. Uyeo, *Chem. Pharm. Bull.* **12** (6), 696 (1964).

<sup>352</sup> S. Kobayashi, M. Kihara, and S. Mineo, *Chem. Pharm. Bull.* **26** (2), 635 (1978).

<sup>353</sup> K. Kotera, M. Motomura, S. Miyazaki, T. Okada, Y. Hamada, R. Kido, K. Hirose, M. Elgyo, H. Jyoyama, and H. Sato, *Shionogi Kenkyusho Nempo* **17**, 88 (1967).

<sup>354</sup> S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.* **23** (1), 3036 (1975).

<sup>355</sup> S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, and H. Matsumoto, *Chem. Pharm. Bull.* **25** (12), 3312 (1977).

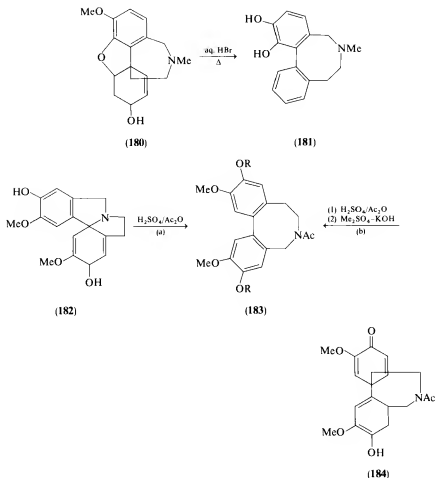
<sup>356</sup> T. Kametani, K. Takahashi, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. C* (10), 1800 (1971).

<sup>357</sup> M. Kihara and S. Kobayashi, *Chem. Pharm. Bull.* **26** (1), 155 (1978).

<sup>358</sup> S. Kobayashi, M. Kihara, and Y. Nakauchi, *Yakugaku Zasshi* **98** (2), 161 (1978).

<sup>359</sup> S. Kobayashi, M. Kihara, and H. Matsumoto, *Yakugaku Zasshi* **98** (2), 863 (1978).

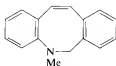




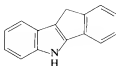
## B. THEORETICAL ASPECTS

Coates and Johnson<sup>255</sup> measured the kinetic acidity of 5-methyl-5,6-dihydrodibenz[*b,f*]azocine (**185**), and found that, when compared to carbocyclic models, **185** evinced very small rate enhancement. Compound **162** exhibited electrochemical behavior similar to that of the 2-benzazocine (i.e., two-electron reduction), but electron addition was more difficult, consistent with the benzannelation effect.<sup>260</sup> Interestingly, **162**, when chemically reduced, undergoes an atypical transannular reaction to give

indole **186**. It was noted that reduction of **162** could not produce the stable  $\text{—N=C(OCH}_3\text{)C}^-$  moiety as did methoxyazocines and methoxybenzazocines.



(185)



(186)

### C. STEREOCHEMISTRY

Examination of the ultraviolet spectrum of a biphenyl type dibenzazocine related to **173** showed that both the short wavelength and conjugation bands were less intense and fell at shorter wavelengths than the corresponding bands for seven-membered bridged biphenyls.<sup>360</sup> This is consistent with an increase in flexibility in the eight-membered ring and the corresponding greater dihedral angle between the benzene rings.<sup>361</sup>

When racemic **173** ( $\text{R} = \text{Me}$ ) was hydrolyzed in the presence of chymotrypsin, the resulting optically active acid **173** ( $\text{R} = \text{H}$ ) exhibited an ORD absorption spectrum characteristic of L-phenylalanine; the starting ester possessed an axially oriented carbomethoxy group.<sup>338,362</sup> Atropisomerism and conformational asymmetry of a precisely definable nature in a substrate are therefore recognized by chymotrypsin. X-ray diffraction studies confirmed that the chymotrypsin-active isomer has an axial ester moiety in the solid state, and that the ester mutarotates in solution to a CD-inactive isomer, whose ester group is in the equatorial position.<sup>363</sup>

The NMR spectra of **187** ( $\text{R} = \text{H, CN, CH}_2\text{Ph}$ ), exhibited typical temperature dependence attributable to an appreciable rotational barrier in the ring.<sup>329</sup> NMR spectrum and strain calculations on **187** ( $\text{R} = \text{CH}_2\text{Ph}$ ) were consistent with the existence of two angle-strain-free conformations **188** and **189**, each of which is capable of inversion.<sup>364</sup> The slowly inverting

<sup>360</sup> E. J. Forbes and C. J. Gray, *Tetrahedron* **24**, 2795 (1968).

<sup>361</sup> See K. Mislow, M. A. W. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, J. Weiss, and C. Djerassi, *J. Am. Chem. Soc.* **84**, 1455 (1962), and references cited therein.

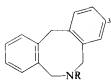
<sup>362</sup> F. Schuber and B. Belleau, *Bioorg. Chem.* **2**, 111 (1973).

<sup>363</sup> Private communication from J. Bordner, R. L. Greene, and G. H. Wahl, Jr.

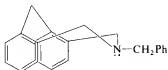
<sup>364</sup> See R. P. Gellatly, W. D. Ollis, and I. O. Sutherland, *J. C. S. Perkin I*, 913 (1976), and references cited therein.

<sup>365</sup> R. N. Renaud, R. B. Layton, and R. B. Fraser, *Can. J. Chem.* **51**, 3380 (1973).

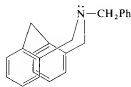
chair **188** predominates over a rapidly inverting mobile boat **189**, the  $E_{act}$  being 17 kcal. Similar results were obtained for **187** ( $R = Me$ ).<sup>364,365</sup> Strain calculation on **187** ( $R = Me$ ) showed that in the boat conformation of such molecules, transannular nonbonded interaction between the benzhydryl  $CH_2$  and the nitrogen results in considerable strain, but that this is attenuated by flattening distortions in the eight-membered ring. Also, several different boat forms are possible, and these were calculated to have similar energies. X-ray diffraction results showing crystalline **187** ( $R = Me$ ) to exist in the chair form were in accord with the above calculations.<sup>366</sup> In another study of solid **187** ( $R = Me$ ), the compound was found by pulsed NMR to exhibit two distinct motions in the solid: methyl reorientation ( $E_{act} \approx 2.1$  kcal) and an unassigned motion, probably nitrogen inversion ( $E_{act} \approx 9.2$  kcal).<sup>367</sup>



(187)

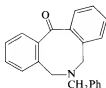


(188) chair (crown)

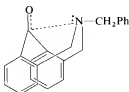


(189) boat (flexible)

Crystalline **187** ( $R = t\text{-Bu}$ ), in contrast to **187** ( $R = Me$ ), was found to exist in a boat conformation.<sup>368</sup> Compound **190** showed a temperature-independent NMR spectrum, the chemical shifts being similar to those of the boat form of **187** ( $R = PhCH_2$ ).<sup>364,369</sup> Transannular attractions of up to 8 kcal, similar to those found in perhydroazocine-5-ones (Section II,D), force **190** into a boat form (**191**).



(190)



(191)

The correlation of geminal coupling constants ( $^2J$ ) of the benzyldryl methylene group with  $\sigma$  values of various substituents at the "3" position

<sup>366</sup> A. D. Hardy and F. R. Ahmed, *Acta Crystallogr., Sect. B* **B30**, 1670 (1974).

<sup>367</sup> D. W. Larsen and T. A. Smentkowski, *J. Magn. Reson.* **28**, 171 (1977) [*CA* **88**, 88664 (1978)].

<sup>368</sup> A. D. Hardy and F. R. Ahmed, *Acta Crystallogr., Sect. B* **B30**, 1674 (1974).

<sup>369</sup> W. D. Ollis, J. F. Stoddart, and I. O. Sutherland, *Tetrahedron* **30**, 1903 (1974), and references cited therein.

of **187** ( $R = \text{Me}$ ) was in accord with the dependence of  $^2J$  on the conformation of the  $\text{CH}_2$  protons with respect to the adjacent rings.<sup>370</sup>

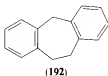
## D. REACTIONS

### 1. Eight-Membered Ring Preserved

N-Substituted derivatives of **170** ( $X = \text{NH}$ ,  $Y = \text{CH}_2$ ) have been prepared by reaction with alkylating agents<sup>371</sup> and  $\text{KCNO}$ ,<sup>372</sup> and by thermal decarboxylation of its N-carbalkoxy derivative.<sup>371</sup>

### 2. Ring Contraction

Compound **170** ( $X = \text{CH}$ ,  $Y = \text{NNTs}$ ), when treated with base, produced dibenzocycloheptadiene **192**.<sup>331</sup>



## E. APPLICATIONS

Dibenzazocines have found a wide application as pharmacological agents. For example, N-substituted dibenzazocines exhibit central nervous system<sup>373-379</sup> antiinflammatory,<sup>380</sup> antihistaminic,<sup>317,381</sup>  $\alpha$ -adrenergic

<sup>370</sup> R. N. Renaud, J. W. Bovenkamp, R. R. Fraser, and R. Cooper, *Can. J. Chem.* **55**, 2642 (1977).

<sup>371</sup> U.S.S.R. Patent 166,614 (1964) [*CA* **62**, 14641 (1965)].

<sup>372</sup> G. Pala, A. Danetti, and A. Montegani, *J. Med. Chem.* **14**, 174 (1971) [*CA* **74**, 76310 (1971)].

<sup>373</sup> Japanese Patent 23,395 (1971) [*CA* **75**, 88508 (1971)].

<sup>374</sup> German Patent 1,180,751 (1965) [*CA* **62**, 13131 (1965)].

<sup>375</sup> British Patent 983,859 (1965) [*CA* **63**, 1775 (1965)].

<sup>376</sup> S. Casadro, G. Pala, E. Crescinzi, E. Marazzi-Ubertio, G. Coppi, and C. Turba, *J. Med. Chem.* **11**, 97 (1968).

<sup>377</sup> W. E. Coyne and J. W. Cusic, *J. Med. Chem.* **11**, 1158 (1968).

<sup>378</sup> Japanese Patent 3,627 (1966) [*CA* **64**, 19579 (1966)].

<sup>379</sup> U.S. Patent 3,489,745 (1970) [*CA* **72**, 111318 (1970)].

<sup>380</sup> U.S. Patent 3,336,293 (1968) [*CA* **68**, 87210 (1968)].

<sup>381</sup> Netherland Patent 3,256 (1966) [*CA* **70**, 47499 (1969)].

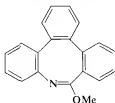
blocking,<sup>382,383</sup> hypotensive,<sup>384</sup> antiarrhythmic,<sup>385</sup> and anticholinesterase<sup>386</sup> activities.

## V. Tribenzazocines and other Fused Azocines

### A. PREPARATION

#### 1. Via Ring Expansion

The only reported synthesis of a tribenzazocine was by Paquette and co-workers, who prepared tribenz[*b,d,f*]azocine (**193**) from tribenztropone



(193)

oxime via the lactam.<sup>260</sup> The following fused ring azocines have also been prepared via the Beckmann rearrangement: cyclopentanolactam **194**,<sup>387,388</sup> indololactams **195**,<sup>389</sup> thienolactams **196** and **197**,<sup>390,391</sup> benzothienolactams **198** and **199**,<sup>392</sup> homobenzazocinones **200** and **201**,<sup>71</sup> and homodibenzazocinone **202**.<sup>71</sup>

<sup>382</sup> Y. Ishida, Y. K. Watanabe, S. Kobayashi, and M. Kihara, *Jpn. J. Pharmacol.* **26** (5), 607 (1976).

<sup>383</sup> Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Chem. Pharm. Bull.* **25** (8), 1851 (1977).

<sup>384</sup> K. Nadzhmutchinov, I. K. Kamilov, and U. B. Zakirov, *Farmakol. Farmakoter. Alkaloidov Glikozidov, Akad. Nauk Uzb. SSR, Khim.-Tekhnol. Biol. Otd.*, 51 (1966).

<sup>385</sup> Kh. U. Ahev and U. B. Zakirov, *Med. Zh. Uzb.* (12), 80 (1969).

<sup>386</sup> Sh. S. Umarova, U. B. Zakirov, and I. K. Kamilov, *Farmakol. Akaloidov Glikozidov*, 103 (1967).

<sup>387</sup> U.S. Patent 3,354,146 (1968) [CA **68**, 29315 (1968)]; Netherland Patent 6,504,369 (1966) [CA **64**, 17446 (1966)].

<sup>388</sup> Japanese Patent 22,495 (1973) [CA **79**, 92190 (1973)].

<sup>389</sup> T. Nagassaka and S. Ohki, *Chem. Pharm. Bull.* **25**, 3023 (1977).

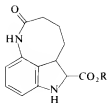
<sup>390</sup> B. D. Fabrichnyi, I. F. Shalavina, and Ya. L. Gol'dfarb, *Zh. Org. Khim.* **3** (11), 2079 (1967).

<sup>391</sup> B. P. Fabrichnyi, I. F. Shalavina, Ya. L. Gol'dfarb, and S. M. Kostrova, *Zh. Org. Khim.* **10** (9), 1956 (1974).

<sup>392</sup> J. M. Bastian, A. Ebnoether, and E. Jucker, *Helv. Chim. Acta* **54** (1), 283 (1971).



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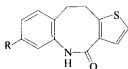
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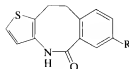
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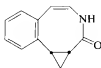
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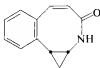
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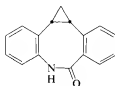
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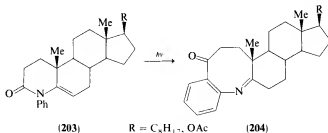


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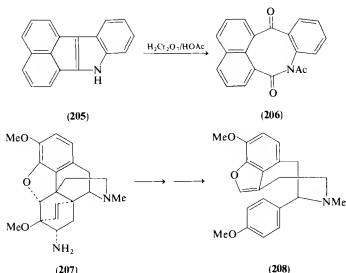
In addition, there are a few non-Beckmann synthetic approaches to fused ring azocines via ring expansion. Irradiation of the *N*-phenyl-4-azasteroids **203** gave the ring expanded products **204**.<sup>393</sup> The naphthoindole **205** could be oxidized with chromic acid to the lactam **206**.<sup>394</sup> Rearrangements of



<sup>393</sup> R. P. Ghandi, M. Singh, Y. P. Sachdera, and S. M. Mukherji, *Tetrahedron Lett.* (9), 661 (1973).

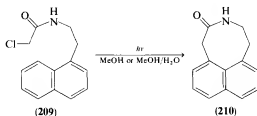
<sup>394</sup> J. B. Duthrie and S. G. P. Plant, *J. Chem. Soc.*, 1899 (1952).

7-substituted-6,14-ethenotetrahydrothebaines yield the furobenzazocine system,<sup>395-397</sup> an example being the conversion of **207** to **208**.<sup>395</sup>



## 2. Via Ring Closure

The naphthazocine **210** was prepared by photolysis of the 1-substituted naphthalene **209**.<sup>398,399</sup> The indololactam **211** was made in a similar manner.<sup>400</sup> Azocinoindoles **213** can also be synthesized via ring closure of



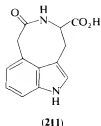
<sup>395</sup> K. W. Bentley, D. G. Hardy, and A. C. B. Smith, *J. Chem. Soc. C* (17), 2235 (1969).

<sup>396</sup> J. W. Lewis, M. J. Readhead, and A. C. B. Smith, *J. C. S. Perkin I* (6), 878 (1972).

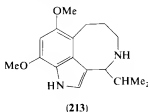
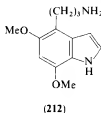
<sup>397</sup> H. Rapoport and P. Sheldrich, *J. Am. Chem. Soc.* **85**, 1636 (1963).

<sup>398</sup> H. M. Ong and E. L. May, *J. Org. Chem.* **35**, 2544 (1970).

<sup>399</sup> C. M. Foltz, *J. Org. Chem.* **36**, 34 (1971).

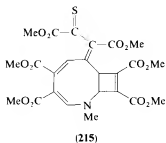
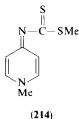


a 4-substituted indole **212** with isobutyraldehyde.<sup>401</sup> The thiophenoazocine **196** ( $R = \text{CO}_2\text{H}$ ), an intermediate in the stereospecific synthesis of biotin, was prepared by cyclization of the appropriate amino acid.<sup>402</sup>



### 3. Via Cycloaddition

The treatment of azocine **44** ( $R^1 = R^2 = \text{Me}$ ) with potassium followed by dichloromethane, afforded homoazocines **49** and **50**. In a similar manner, **137** and **138** yielded **142** and **141**, respectively.<sup>71</sup> The reaction of the 1,4-dihydropyridine **214** with two equivalents of dimethylacetylene carboxylate gave the cyclobutenoazocine **215**.<sup>403</sup>



<sup>400</sup> O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.* **88**, 3941 (1966).

<sup>401</sup> U.S. Patent 3,904,645 (1976) [C.A. **84**, 44004 (1976)].

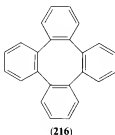
<sup>402</sup> P. N. Confalone, G. Pizzolato, and M. R. Uskokovic, *J. Org. Chem.* **42**, 135 (1977).

<sup>403</sup> K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles* **4**, 705 (1976).



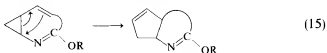
## B. THEORETICAL AND STEREOCHEMICAL CONSIDERATIONS

6-Methoxytribenz[*b,d,f*]azocine **193** does not undergo the electrochemical or chemical reduction typical of other azocines.<sup>260</sup> This was attributed mainly to steric hindrance to planarity, a phenomenon not surprising in view of the extremely high inversion barrier in tetrabenzocyclooctatetraene (**216**).<sup>404</sup>

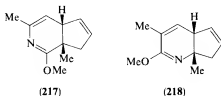


## C. REACTIONS

Homoazocines **49** and **50** (Section V.A) undergo thermal rearrangement to 3-azabicyclo[4.3.0]nonanes **217** and **218**, respectively,<sup>405</sup> most likely via a concerted or diradical [1,3]-sigmatropic "vinylcyclopropane" shift (Eq. 15),



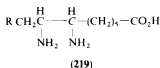
in which the strongly stabilized imide function is not deconjugated.



<sup>404</sup> P. W. Rabideau, *Diss. Abstr. Int. B* **30**, 4059 (1970); A. Rosedahl and S. Sandstrom, *Tetrahedron Lett.*, 4187 (1972); D. Gust, G. H. Senkler, Jr., and K. Mislow, *J. C. S. Chem. Commun.*, 1345 (1972); C. J. Finder, D. Chung, and N. L. Allinger, *Tetrahedron Lett.*, 4677 (1972).

<sup>405</sup> G. D. Ewing, S. V. Ley, and L. A. Paquette, *J. Am. Chem. Soc.* **100**, 2909 (1978).

The amide position on the thiophenolactams **196** and **197** has been spectroscopically distinguished from the corresponding caprolactams.<sup>406,407</sup> Nitration of **196** (R = alkyl), followed by reductive desulfurization, gave a substituted enantholactam, which could be hydrolyzed to diamino acids **219**. These compounds, when treated with urea, gave 5-alkyl-2-oxo-4-imidazolinealkanoic acids similar to those with known biotin or antibiotin activity.<sup>408</sup>



#### D. APPLICATIONS

Indoloazocines are useful as central nervous system depressants<sup>409</sup> and also have shown some melatonin activity.<sup>410</sup> Benzo[*g*]thieno[3,2-*c*]azocines have been employed as antidepressants.<sup>411</sup>

<sup>406</sup> Y. L. Gol'dfarb, I. P. Yakovlev, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1011 (1970) [*CA* **73**, 76348 (1970)].

<sup>407</sup> Y. L. Gol'dfarb, B. M. Zolotarev, V. I. Kadentsev, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1014 (1970) [*CA* **73**, 76370 (1970)].

<sup>408</sup> B. P. Fabrichnyi, I. F. Shalavina, S. M. Kostrova, and Y. L. Gol'dfarb, *Zh. Org. Khim.*, **6**, 1091 (1970); *J. Org. Chem. USSR (Engl. Transl.)*, **6**, 1093 (1970), and references cited therein.

<sup>409</sup> U.S. Patent 3,637,744 (1972) [*CA* **76**, 113194 (1972)].

<sup>410</sup> T. Kobayashi, T. F. Spande, H. Aoyagi, and B. Witkop, *J. Med. Chem.*, **12**, 636 (1969).

<sup>411</sup> Swiss Patent 481,139 (1970) [*CA* **72**, 90423 (1970)].

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## Dewar Heterocycles and Related Compounds

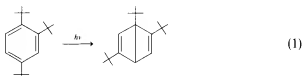
YOSHIRO KOBAYASHI AND ITSUMARO KUMADAKI

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## I. Introduction

Advances in photochemistry stimulated studies on valence-bond isomers of benzene. The first valence-bond isomer of a substituted benzene was isolated by van Tamelen and a co-worker in 1962<sup>1</sup> (Eq. 1), and since then many valence-bond isomers have been isolated or postulated as intermediates in photoreactions.



<sup>1</sup> E. E. van Tamelen and S. P. Pappas, *J. Am. Chem. Soc.* **84**, 3789 (1962).

Since the late 1960s photoreactions of heterocyclic compounds have been investigated extensively. Valence-bond isomers have been proposed as intermediates, but their isolations have succeeded only in the last 10 years. In this review, we shall consider the valence-bond isomers of heterocyclic compounds having four-membered rings: Dewar heterocycles.

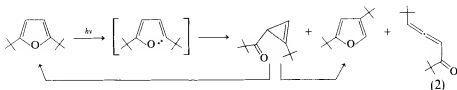
This chapter is limited to reactants that have five- and six-membered rings incorporating oxygen, sulfur and/or nitrogen atoms. Because the number of Dewar heterocycles that have been isolated is very limited we also shall show some reactions where Dewar heterocycles were postulated as intermediates. Interestingly, most of the isolated Dewar heterocycles are substituted with perfluoroalkyl groups. The stabilizing effect of perfluoroalkyl groups on the isolation of sterically hindered compounds has been discussed.<sup>2</sup> Theoretical considerations of structure and reactivity of Dewar heterocycles based on molecular orbital theory will be included.

## II. Dewar Isomers of Five-Membered Heterocycles with One Heteroatom

The photoreactions of five-membered heterocycles with one heteroatom give structural isomers. In some cases Dewar isomers were proposed as intermediates, but only a small number were isolated.

### A. PHOTOREACTIONS OF FURANS

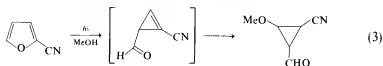
No Dewar furan has been isolated or observed spectrometrically. Van Tamelen, who first isolated Dewar benzene substituted with *t*-butyl groups, examined the photolysis of di- and tri-*t*-butylfurans to compare results with those for the benzene. In the photoreaction of 2,5-di-*t*-butylfuran, three isomers were isolated (Eq. 2), including a cyclopropenyl ketone but not a Dewar furan.<sup>3</sup>



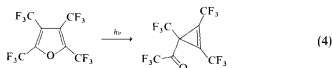
<sup>2</sup> D. M. Lemal and L. H. Dunlap, Jr., *J. Am. Chem. Soc.* **94**, 6562 (1972); A. Greenberg, J. F. Liebman, and D. Van Vechten, *Tetrahedron* **36**, 1161 (1980); Y. Kobayashi and I. Kumadaki, *Acc. Chem. Res.* **14**, 76 (1981).

<sup>3</sup> E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *J. Am. Chem. Soc.* **93**, 6129 (1971).

The photoreaction of 2-cyanofuran in methanol gave an adduct of the cyclopropenylaldehyde intermediate with methanol (Eq. 3).<sup>4</sup>



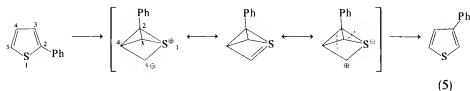
Perfluorotetramethylfuran, though it has four trifluoromethyl groups to stabilize valence-bond isomers, gave only a cyclopropenyl ketone (Eq. 4).<sup>5</sup>



Thus, furan derivatives seem to isomerize to cyclopropenylcarbonyl compounds in photoreactions. However, recently Lemal informed us that Dewar furan was derived from tetrakis(trifluoromethyl)Dewar thiophene (II B).

## B. PHOTOREACTIONS OF THIOPHENES

Photoisomerization of 2-arylthiophene to 3-arylthiophene was reported by Wynberg *et al.*<sup>6</sup> Initially, they proposed a tricyclic intermediate (Eq. 5). But, since this mechanism could not explain all the minor products, many investigations were carried out.

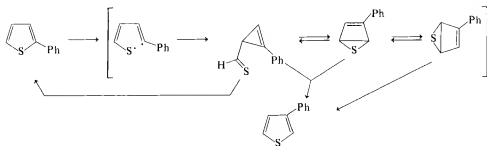


Van Tamelen proposed another mechanism for this isomerization involving an equilibrium among the cyclopropenyl thio ketone and Dewar structures (Scheme 1).<sup>3</sup>

<sup>4</sup> H. Hiraoka, *J. C. S. Chem. Commun.*, 1610 (1971).

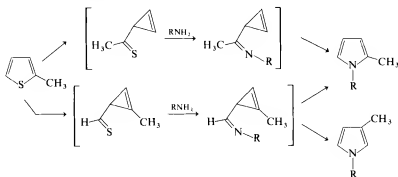
<sup>5</sup> R. D. Chambers, A. A. Lindley, and H. C. Fielding, *J. Fluorine Chem.* **12**, 337 (1978).

<sup>6</sup> H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhs, *J. Am. Chem. Soc.* **89**, 3501 (1967), and references therein.



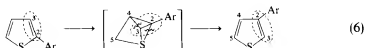
SCHEME 1

Couture showed that methyl- and dimethylthiophene on irradiation in a primary amine gave pyrroles and proposed a mechanism where the first step is the formation of a thioketone or a thioaldehyde by analogy with furan photochemistry (Scheme 2).<sup>7</sup>



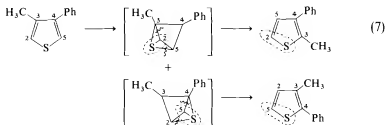
SCHEME 2

Kellogg proposed a new model for the excited structure where a two-atom fragment is rotated 90° out of the plane formed by the remaining three atoms (Eqs. 6 and 7).<sup>8</sup> The two-atom fragment is encircled. Again, no intermediate was observed.

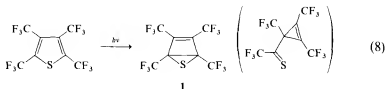


<sup>7</sup> A. Couture and A. Lablache-Combiér, *Tetrahedron* **27**, 1159 (1971).

<sup>8</sup> R. M. Kellogg, *Tetrahedron Lett.*, 1429 (1972).



Irradiation of tetrakis(trifluoromethyl)thiophene gave a valence-bond isomer which Hecklen first proposed to have a Dewar structure,<sup>9</sup> then a cyclopropenyl thio ketone,<sup>10</sup> and still later<sup>11</sup> a Dewar form. The structure was shown to be Dewar form **1** by <sup>19</sup>F and <sup>13</sup>C NMR and by the study of its reactions (Eq. 8).<sup>12-14</sup> This is the first isolated example of a Dewar isomer of a five-membered heterocycle.



In spite of its highly strained Dewar structure **1** is stable and may be kept in a refrigerator for several years. It isomerizes to the aromatic isomer at high temperature (half-life in benzene at 160°C was 5.1 h). The treatment of the Dewar thiophene with triphenylphosphine did not cause the elimination of sulfur, but instead accelerated the isomerization to the aromatic isomer. This catalytic acceleration is limited to trivalent phosphorus compounds but phosphorous trichloride or phenyldichlorophosphine are ineffective. An adduct of diphenylchlorophosphine with the Dewar thiophene was postulated to be a  $\sigma$ -complex with a P—S bond. It decomposed spontaneously to the thiophene and the phosphine as shown in Eq. (9).<sup>15</sup> Recently,

<sup>9</sup> H. A. Wiebe, S. Braslavsky, and J. Hecklen, *Can. J. Chem.*, **48**, 164-70, p. 1 (1970).

<sup>10</sup> E. Wu and J. Hecklen, *J. Am. Chem. Soc.*, **93**, 3432 (1971).

<sup>11</sup> H. A. Wiebe, S. Braslavsky, and J. Hecklen, *Can. J. Chem.*, **50**, 2721 (1972).

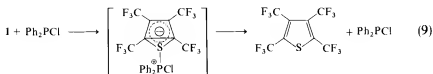
<sup>12</sup> Y. Kobayashi, A. Ohsawa, Y. Sekine, and I. Kumadaki, *93rd Ann. Meet. Pharm. Soc. Jpn.*, 1973, Abstracts, Part II, p. 146.

<sup>13</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, and Y. Sekine, *Tetrahedron Lett.*, 2841 (1974).

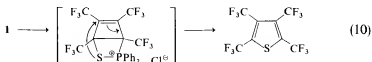
<sup>14</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, Y. Sekine, and H. Mochizuki, *Chem. Pharm. Bull.*, **23**, 2773 (1975).

<sup>15</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, and Y. Sekine, *Tetrahedron Lett.*, 1639 (1975).

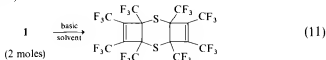




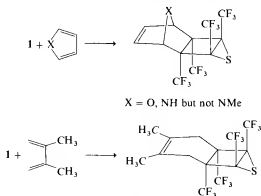
Lemal<sup>16</sup> proposed another structure for the complex (Eq. 10) based on P—F couplings. However, these couplings seem to be too small to support a P—C—C—F structure and their intermediate seems likely to lose phosphine thioxide.



Dewar thiophene **1** dimerized to a dicyclobutadithian compound in a basic solvent (Eq. 11).<sup>14</sup>



The cyclobutenyl double bond of Dewar thiophene (**1**) is a good dienophile, since it is highly strained and substituted with trifluoromethyl groups of high electronegativity. It reacts with many cyclic and acyclic dienes as shown in Scheme 3.<sup>17</sup> Substituents on the bridge parts of cyclic



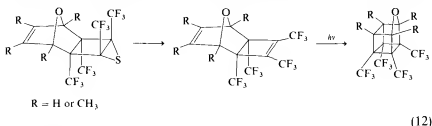
SCHEME 3

<sup>16</sup> D. M. Lemal, "The Second Chemical Conference of the North American Continent, August 1980, Las Vegas, Nevada," Abstr. Pap. Am. Chem. Soc., Washington, D.C., 1980

<sup>17</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, Y. Sekine, and A. Ando, *J. C. S. Perkin I*, 2355 (1977).

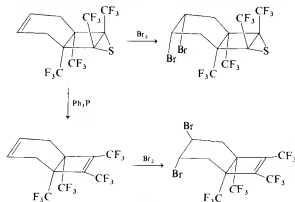
dienes or those on the terminal position of acyclic dienes inhibit the reaction strongly because steric repulsion between the  $\text{CF}_3$  groups and the substituents control the reaction. The transition state has an *exo-anti* form as indicated by the fact that 2,3-dimethylbutadiene reacts much faster than butadiene. This was determined by X-ray analysis.<sup>18</sup>

The cycloadducts with furans are especially interesting because they may be converted to oxahomocubanes<sup>13</sup> by desulfurization with triphenylphosphine followed by photolysis (Eq. 12). The photocyclization is also interesting,



because the *exo* compound cyclizes intramolecularly. Since this reaction is not affected by a sensitizer or a radical scavenger, the required *syn* intermediate might be formed through a singlet elimination-addition or ring-opening-recyclization process.<sup>13,14</sup>

Dewar structure **1** forms a cycloadduct with butadiene. Bromination of this adduct gives a *cis* dibromide. *Cis* bromination may be attributed to a steric effect of the two trifluoromethyl groups on the thiirane ring. If desulfurization precedes bromination, then the addition gives a *trans* dibromide (Scheme 4). The latter pathway provides access to tetrakis(trifluoromethyl)-

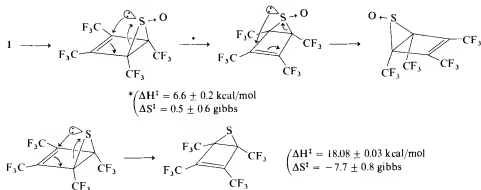


SCHEME 4

<sup>18</sup> N. Kikutani, Y. Iitaka, Y. Kobayashi, I. Kumadaki, A. Ohsawa, and Y. Sekine, *Acta Crystallogr., Sect. B* **31**, 1478 (1975).

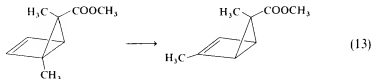
cyclooctatetraene which provides entry into some interesting semibullvalene chemistry.<sup>19,20</sup>

The Dewar thiophene **1** was oxidized to its *S*-Oxide. <sup>19</sup>F NMR of the latter compound showed an automerization through the 1,3-shift of the *S*-oxide group.<sup>21</sup> Later, the Dewar thiophene itself was found to automerize at much higher temperature.<sup>22</sup> The lone pair on the sulfur atom was proposed to participate in the 1,3-shift. Lemal named it a pseudopericyclic reaction (Scheme 5). The bond order between the lone pair and the C—C double



SCHEME 5

bond was estimated to be 0.06 before any distortion. This fact seems to support the above mechanism. On the other hand, some bicyclopentenenes, which have no lone pair electrons, isomerized by the similar walk mechanism (Eq. 13). The driving force for this reaction was attributed to internal strain.<sup>23</sup>



Recently, it was shown that MO calculations could not distinguish between a "four-electron" pericyclic and a "six-electron" pseudopericyclic transition state.<sup>24</sup>

<sup>19</sup> Y. Kobayashi, A. Ando, K. Kawada, and I. Kumadaki, *J. Chem. Soc., Chem. Commun.*, 1289 (1981).

<sup>20</sup> Y. Kobayashi, A. Ando, K. Kawada, and I. Kumadaki, *J. Am. Chem. Soc.* **103**, 3958 (1981).

<sup>21</sup> J. A. Ross, R. P. Seiders, and D. M. Lemal, *J. Am. Chem. Soc.* **98**, 4325 (1976).

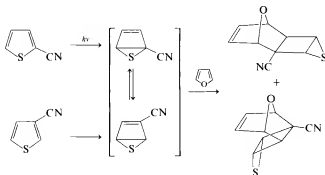
<sup>22</sup> C. H. Bushweller, J. A. Ross, and D. M. Lemal, *J. Am. Chem. Soc.* **99**, 629 (1977).

<sup>23</sup> F.-G. Klärner and F. Adamsky, *Angew. Chem.* **91**, 738 (1979).

<sup>24</sup> J. P. Snyder and T. A. Halgren, *J. Am. Chem. Soc.* **102**, 2861 (1980).

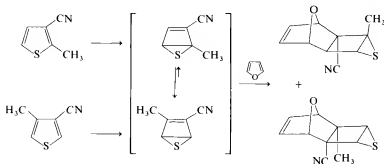
Dewar thiophene **1** is the first authentic example of such a structure. Its high stability suggests that the electronic structure may be strongly perturbed by the trifluoromethyl groups. Therefore, the isomerization of other thiophenes may not always pass through the Dewar intermediate.

A recent study showed that the irradiation of 2- or 3-cyanothiophene in the presence of furan gave endo and exo Diels–Alder adducts of Dewar 3-cyanothiophene with furan in the same proportion (Scheme 6). This result



SCHEME 6

suggested the intervention of the Dewar structure and the isomerization by walk mechanism of the sulfur atom.<sup>25</sup> The adduct may be formed from the more reactive 2-cyano-5-thiabicyclopentene. Further, the irradiation of 3-cyano-2-methyl- or 3-cyano-4-methylthiophene gave low yields of 2-cyano-3-methyl-5-thiabicyclopentene, which underwent the Diels–Alder reaction with furan to give a 1:1 mixture of exo and anti isomers with traces of endo isomers (Scheme 7). In this case, only 2-cyano-3-methyl-5-thiabicyclopentene

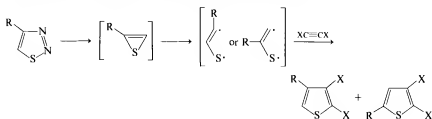


SCHEME 7

<sup>25</sup> J. A. Barltrop, A. C. Day, and E. Irving, *J. C. S. Chem. Commun.*, 881 (1979).

was observed by NMR; the equilibrium between the Dewar thiophenes is in favor of this isomer, probably due to conjugation of the cyano and the methyl groups<sup>26</sup> (see Section IV,E). 1-Cyano-5-thiabicyclopentene was observed at low temperature, but it isomerized rapidly to the 2-cyano isomer or the aromatic counterpart. These results support the walk mechanism of the Dewar type intermediate. The transition state of the walk mechanism by Lemal seems to have some similarities to Wynberg's intermediate. Therefore, substituents seem to play a very important role in determining the reaction mechanism; some may stabilize the bicyclic intermediate and others seem to make the tricyclic one stable and allow it to convert to the aromatic counterpart directly.

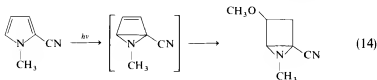
Another approach to Dewar thiophene is  $[2 + 2]$  cycloaddition of a thiirene and an acetylene, but this reaction proceeds through the ring opening of the thiirene followed by cycloaddition (Scheme 8).<sup>27</sup>



SCHEME 8

### C. SYNTHESIS AND REACTIONS OF DEWAR PYRROLES

The formation of pyrroles by the photolysis of furan or thiophene in the presence of a primary amine was considered to involve valence-bond isomers of pyrroles but the latter were not isolated. However, the photoreaction of cyanopyrrole was examined at the same time as that of cyanofuran (Section I,A), and much earlier than that of cyanothiophenes (Section I,B). Irradiation of 2-cyano-1-methylpyrrole in methanol was reported to give 1-cyano-3-methoxy-5-methyl-5-azabicyclo[2.1.0]pentane, which may have been formed from the Dewar compound (Eq. 14).<sup>4</sup> The structure of the



<sup>26</sup> J. A. Barltrop, A. C. Day, and E. Irving, *J. C. S. Chem. Commun.*, 966 (1979).

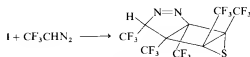
<sup>27</sup> A. Krantz and J. Laurenzi, *J. Am. Chem. Soc.*, **103**, 486 (1981), and references therein.



Dewar thiophene **1** adds an azide to give **2**, which was denitrogenated by irradiation with a mercury lamp to aziridines (**3**).<sup>29,30</sup> Compounds **3** were desulfurized to Dewar pyrroles (**4**). Dewar *N*-phenylpyrrole (**4**, R = Ph) isomerized spontaneously by a (3,3) sigmatropic reaction to a cyclobutaindole compound (**5**), while others (**4**, R ≠ Ph) were fairly stable at room temperature,<sup>29,30</sup> but gradually isomerized to aromatic counterparts (**6**) on heating or irradiation with a mercury lamp.<sup>31</sup> Since the photoisomerization of **4** to **6** was fairly fast, the photoisomerization of **6** to **4** could not be observed, but the photolysis of **6** (R = Ph) gave the cyclobutaindole (**5**) slowly. This fact suggests that an equilibrium between **4** and **6** was present on irradiation, and that a part of **4** isomerized thermally to **5**.<sup>32,33</sup> This is the second support for the intervention of the Dewar pyrrole in the photo-reaction of pyrrole. However, any evidence of a walk of the N—R part of **4** was not observed by NMR over a wide range of temperature.

The desulfurization of the adducts (**2**) with triphenylphosphine gave cyclobutatriazolines (**7**), which on photolysis gave the Dewar compound **4** (R = C<sub>6</sub>H<sub>11</sub>).

Reaction of Dewar thiophene **1** with trifluoromethyldiazomethane gives an adduct which was desulfurized and pyrolyzed to tetrakis(trifluoromethyl)pyrrole, among other products (Scheme 11).<sup>34,35</sup>



SCHEME 11

Another synthesis of a trifluoromethylated Dewar pyrrole involves a valence-bond isomer of a diazepine.<sup>36</sup> The thermolysis of 1,3,4,5,6-pentakis-(trifluoromethyl)-2,4-diazabicyclo[3.2.0]hepta-2,6-diene gave tetrakis-(trifluoromethyl)pyrrole possibly through a (3,3) sigmatropic recyclization followed by the elimination of trifluoroacetonitrile. The thermolysis of the *N*-methyl derivative gave a Dewar isomer, which was fairly stable even at 200°C. These reactions are summarized in Scheme 12.

<sup>30</sup> Y. Kobayashi, A. Ando, K. Kawada, A. Ohsawa, and I. Kumadaki, *J. Org. Chem.* **45**, 2962 (1980).

<sup>31</sup> Y. Kobayashi, A. Ando, K. Kawada, and I. Kumadaki, *J. Org. Chem.* **45**, 2966 (1980).

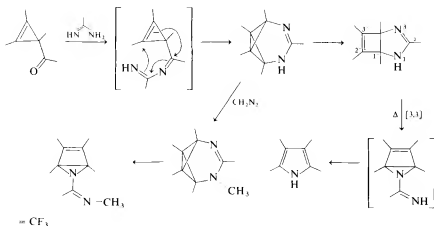
<sup>32</sup> Y. Kobayashi, A. Ando, K. Kawada, and I. Kumadaki, *J. Org. Chem.* **45**, 2968 (1980).

<sup>33</sup> A. Couture, A. Delevallee, A. Lablache-Combier, and C. Parkanyl, *Tetrahedron* **31**, 785 (1975).

<sup>34</sup> E. D. Laganis and D. M. Lemal, *J. Am. Chem. Soc.* **102**, 6633 (1980).

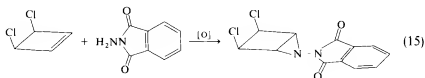
<sup>35</sup> E. D. Laganis and D. M. Lemal, *J. Am. Chem. Soc.* **102**, 6634 (1980).

<sup>36</sup> T. Nakano, Dissertation Thesis, Tokyo College of Pharmacy (1981).



SCHEME 12

A possible approach to Dewar pyrroles is shown in Eq. (15). However, the dechlorination of the product was not reported.<sup>37</sup>



The isolation of a Dewar pyrrole in the photolysis of a pyrrole has not been reported, but the isolation of the trapped intermediate as its adduct with methanol or furan<sup>28</sup> and the photoreaction of *N*-phenyltetrakis(trifluoromethyl)pyrrole<sup>32</sup> strongly support the intervention of Dewar pyrroles in the photoreaction. However, not enough data are available to say which substituents will give a Dewar pyrrole.









Some Dewar tetrakis(trifluoromethyl)pyrroles react as dienophiles. Their reactivities depend on the substituent on the nitrogen atom. A few reactions are shown in Table I, with the results of the Dewar thiophene analog for comparison. Interestingly, *N*-unsubstituted Dewar pyrrole is the most and the *N*-cyclohexyl compound the least reactive of the three. These results seem to indicate a steric requirement in the transition states.

The dramatic difference in reactivity between the two Dewar pyrroles certainly reflects a buttressing effect between the *N*-cyclohexyl and the

<sup>37</sup> A. G. Anderson, Jr. and D. R. Fagerberg, *Tetrahedron* **29**, 2973 (1973).



TABLE I  
REACTIVITY OF DEWAR COMPOUNDS IN DIELS-ALDER REACTIONS AT  
ROOM TEMPERATURE

			
	30 min 49% <sup>b</sup>	30 min 61%	30 min 95%
	30 min 30% <sup>b</sup>	25 min 81%	30 min 73%
	1 hr 83%	1-2 days 78%	3 weeks 76%
	15 hr 59%	7 days 75%	7 days no reaction
	2 weeks 66%	7 days no reaction	—

<sup>a</sup> R = CF<sub>3</sub>, R' = CH<sub>3</sub>.

<sup>b</sup> High sublimability lowered the yield of product.

trifluoromethyl group which makes rehybridization as found in the cycloaddition product more difficult (Fig. 1).<sup>38</sup>

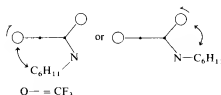


FIG.1 Schematic explanation of reactivity

### III. Dewar Isomers of Five-Membered Heterocycles with More than One Heteroatom

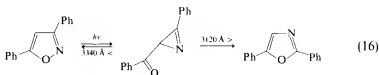
Many photochemical isomerizations of five-membered heterocycles having two or more heteroatoms including ring transformations have been

<sup>38</sup> Y. Kobayashi, A. Ando, and I. Kumadaki, unpublished data.

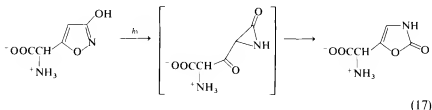
reported, but Dewar compounds with two or more heteroatoms have not been isolated except those of mesoionic compounds, such as sydnones. Ring transformation on irradiation will be discussed first followed by some reactions of the mesoionic compounds.

### A. PHOTOREACTIONS OF OXAZOLES AND ISOXAZOLES

The photochemical transformation of an isoxazole to an oxazole was reported early in the 1960s and was found to involve not a Dewar, but an azirin intermediate, which could be isolated (Eq. 16).<sup>39</sup> The isomerization of the azirin was dependent on the wavelength. Thus, the isomerization to the isoxazole was achieved by a light of wavelength longer than 3340 Å, while that to the oxazole shorter than 3120 Å. These facts suggested that the former is a triplet and the latter a singlet reaction.



A similar reaction was used for the synthesis of muscazone from ibotenic acid (Eq 17).<sup>40</sup> Only the 2 and 3 positions interchange.

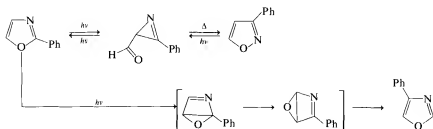


On the other hand, the photoisomerization of oxazoles to isoxazoles involves not only the interchange of the 2 and 3 positions, but that of the 2 and 4 positions. To explain the latter reaction, the intervention of a Dewar compound was proposed (Scheme 13).<sup>41</sup> The walk of the oxygen atom is characteristic of this mechanism. A quantum mechanical calculation suggested that the O—C-2 bond was weak (for the azirin) and the bond order between C-2 and C-5 was high (for the Dewar intermediate) in the excited state.

<sup>39</sup> B. Singh and E. F. Ullman, *J. Am. Chem. Soc.* **89**, 6911 (1967).

<sup>40</sup> H. Göth, A. R. Gagneux, C. H. Eugster, and H. Schmidt, *Helv. Chim. Acta* **50**, 137 (1967).

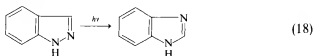
<sup>41</sup> M. Maeda and M. Kojima, *J. C. S. Perkin I*, 239 (1977), and references therein.



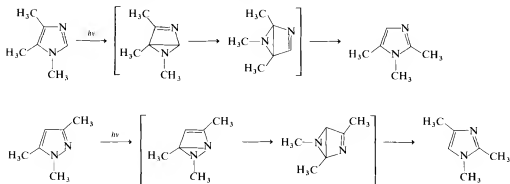
SCHEME 13

### B. PHOTOREACTIONS OF PYRAZOLES AND IMIDAZOLES

Indazole may be photoisomerized to benzimidazole (Eq. 18).<sup>42</sup> A similar



interconversion between pyrazoles and imidazoles was observed later and an azirin mechanism was proposed. However, as in the case of oxazoles, the interchange between the 2 and 4 positions was also observed, and the walk mechanism involving Dewar intermediates was proposed (Scheme 14).<sup>43</sup> Dewar intermediates were not isolated, but bicyclic compounds from 3*H*-pyrazoles were reported (Eq 19).<sup>44</sup>

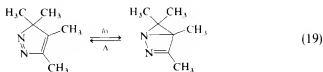


SCHEME 14

<sup>42</sup> H. Tiefenhaler, W. Dörscheln, H. Göth, and H. Schmidt, *Tetrahedron Lett.*, 2999 (1964).

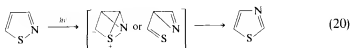
<sup>43</sup> P. Beak, J. L. Miesel, and W. R. Messer, *Tetrahedron Lett.*, 5315 (1967).

<sup>44</sup> W. J. Leigh and D. R. Arnold, *Can. J. Chem.*, **57**, 1186 (1979).

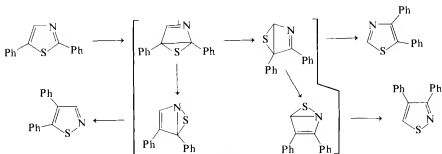


## C. PHOTOREACTIONS OF THIAZOLES AND ISOTHAZOLES

Photoisomerization of isothiazole to thiazole was reported (Eq. 20).<sup>45</sup> The intermediate was proposed to be a valence-shell extended one comparable to that proposed by Wynberg or an azirin. Reverse isomerization of thiazole to isothiazole was not observed.



In order to determine whether the thiazole ring can be photorearranged the photoreactions of diphenylthiazoles were examined. A variety of isomers do result. Since the formation of all the products was not explained by the two intermediates shown in Eq. (20), the walk of the sulfur atom in the Dewar intermediates were proposed, as shown in Scheme (15). In this case, the intervention of still other valence-shell extended intermediates could not be ruled out.<sup>46</sup>

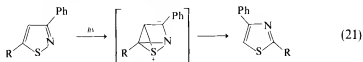


SCHEME 15

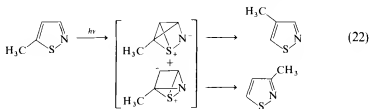
<sup>45</sup> J. P. Catteau, A. Lablache-Combier, and A. Pollet, *J. C. S. Chem. Commun.*, 1018 (1969).

<sup>46</sup> M. Kojima and M. Maeda, *J. C. S. Chem. Commun.*, 386 (1970).

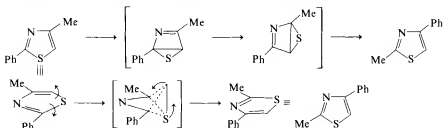
A dipolar intermediate with a valence-shell extension was proposed for the photoisomerization of phenyl isothiazoles (Eq. 21).<sup>47</sup>



The difference between such valence-shell extended intermediates and those proposed by Wynberg for his reactions is the presence of the 2,4 bonding or the 2,5 bonding. Significantly, the photoisomerization of methylisothiazoles depends on the polarity of the solvents, an observation which supports the suggested formation of zwitterionic intermediates (Eq. 22).<sup>48</sup>



The isomerization of methylphenyl thiazoles and isothiazoles was extensively studied. The formation of bicyclic intermediates or the bond-switching mechanism proposed for thiophene was assumed (Scheme 16).<sup>49</sup>



SCHEME 16

More recently, deuterium exchange during the course of the photoisomerization was examined. A mechanism having tricyclic intermediates was proposed (Scheme 17).<sup>50</sup> The mesoionic intermediates having the negative

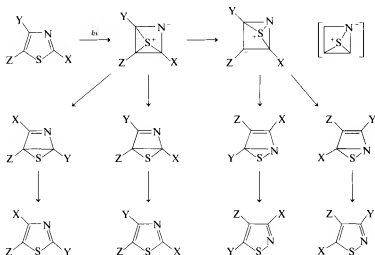
<sup>47</sup> M. Ohashi, A. Iio, and T. Yonezawa, *J. C. S. Chem. Commun.*, 1148 (1970).

<sup>48</sup> A. Lablache-Combier and A. Pollet, *Tetrahedron* **28**, 3141 (1972).

<sup>49</sup> C. Riou, J. C. Poite, G. Vernin, and J. Metzger, *Tetrahedron* **30**, 879 (1974), and references therein.

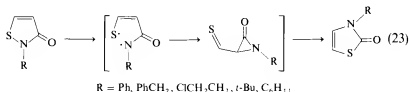
<sup>50</sup> M. Maeda and M. Kojima, *J. C. S. Perkin I*, 685 (1978).

charge on the carbon atom adjacent to the nitrogen (shown in brackets) should not be considered. Further, in the step from the tricyclic to the bicyclic compound, the bond to the carbon atom substituted with a phenyl group was preferably cleaved.



SCHEME 17

In the isomerization of isothiazolone to thiazolone, a three-membered intermediate through a radical mechanism was proposed (Eq. 23).<sup>51</sup>

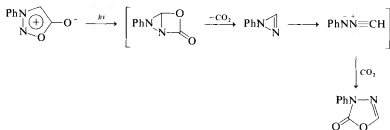


#### D. PHOTOREACTIONS OF MESOIONIC FIVE-MEMBERED HETEROCYCLES

The mesoionic compounds, such as sydnone, are not pure aromatic compounds of a classical sense, but their photoreactions give bicyclic intermediates having four-membered rings which are very useful for the syntheses of new compounds. Thus, some of these reactions will be presented.

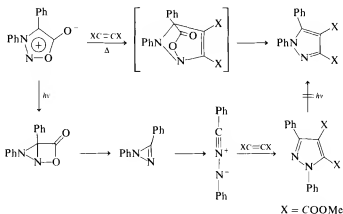
<sup>51</sup> J. Rokach and P. Hamel, *J. C. S. Chem. Commun.*, 786 (1979).

The photoisomerization of *N*-phenylsydnone to 4-phenyl-1,3,4-oxadiazolinone was reported to involve a bicyclic intermediate which eliminated and then readded carbon dioxide (Scheme 18).<sup>52</sup> Labeled carbon dioxide was incorporated.



SCHEME 18

While thermal cycloadditions of sydnone with acetylenes are well known, the photolysis of sydnone in the presence of acetylenes gives different products (Scheme 19).<sup>53</sup>



SCHEME 19

The three-membered intermediate was very liable to open to a dipolar compound. Therefore, cyclopentadiene reacted not as a diene but as a dipolarophile (Scheme 20).<sup>54,55</sup>

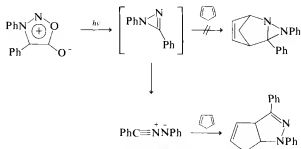
A similar bicyclic intermediate was proposed for the photoisomerization of a mesoionic triazolone compound, but the bicyclic intermediate was not

<sup>52</sup> C. H. Krauch, J. Kuhls, and H.-J. Piek, *Tetrahedron Lett.*, 4043 (1966).

<sup>53</sup> C. S. Angadiyavar and M. V. George, *J. Org. Chem.* **36**, 1589 (1971).

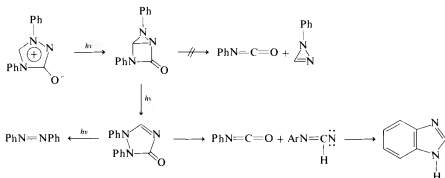
<sup>54</sup> H. Gotthardt and F. Reiter, *Chem. Ber.* **112**, 1206 (1979).

<sup>55</sup> H. Gotthardt and F. Reiter, *Chem. Ber.* **112**, 1635 (1979).



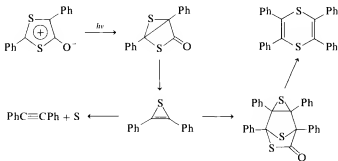
SCHEME 20

cleaved to a diazirin; instead it recycled to a nonionic triazolone, which further cleaved.<sup>56</sup>



SCHEME 21

A mesoionic dithiolone was photolyzed through a bicyclic intermediate, which cleaved to a thiirene. The thiirene added to the starting material and the adduct recycled to a dithiin (Scheme 22).<sup>57</sup>



SCHEME 22

<sup>56</sup> H. Kato, T. Shiba, E. Kitajima, and T. Kiyosawa, *J. C. S. Perkin I*, 863 (1976).

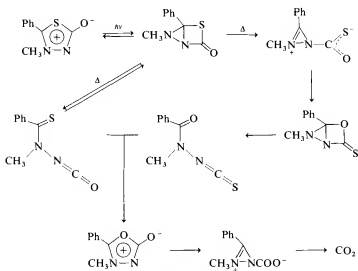
<sup>57</sup> H. Kato, M. Kawamura, and T. Shiba, *J. C. S. Chem. Commun.*, 959 (1970).



In the photolysis of a mesoionic dithioloneimine, a bicyclic intermediate recycled to a nonionic isomer (Eq. 24).<sup>58</sup>



The photoreaction of a mesoionic thiadiazolone gave *N*-isocyanatothionamide, which further converted to *N*-isothiocyanatoamide as shown in Scheme 23.<sup>59</sup>



SCHEME 23

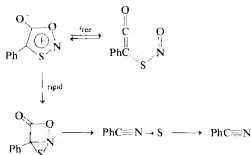
This type of reaction was found to be affected by the mobility of the molecule in the medium. Therefore, a mesoionic oxathiazolone in both a free and rigid state was photolyzed, the former giving ketene and the rigid state a bicyclic intermediate (Scheme 24).<sup>60,61</sup>

<sup>58</sup> J. M. Coxon, M. P. Hartshorn, and C. N. Muir, *J. C. S. Chem. Commun.*, 1591 (1970).

<sup>59</sup> R. M. Moriarty, R. Mukherjee, O. L. Chapman, and D. R. Eckroth, *Tetrahedron Lett.*, 397 (1971).

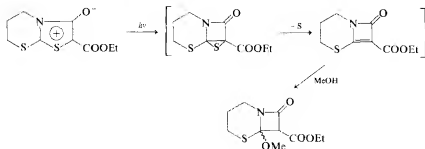
<sup>60</sup> A. Holm, N. Harrit, K. Bechgaard, O. Buchardt, and S. E. Harnung, *J. C. S. Chem. Commun.*, 1125 (1972).

<sup>61</sup> I. R. Dunkin, M. Poliakoff, J. J. Turner, N. Harrit, and A. Holm, *Tetrahedron Lett.*, 873 (1976).



SCHEME 24

In the above reactions, a bicyclic intermediate having fused three and four-membered rings is cleaved. Elimination of the sulfur atom from the three-membered ring was used for the synthesis of a  $\beta$ -lactam (Scheme 25).<sup>6,2</sup>



SCHEME 25

#### IV. Dewar Isomers of Six-Membered Heterocycles

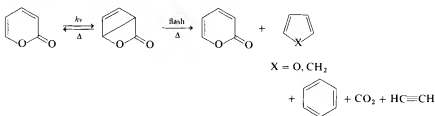
A Dewar isomer of unsubstituted pyridine was identified by Wilzbach, but it was very unstable.<sup>6,3</sup> Other Dewar isomers of six-membered heterocycles, isolated and fairly stable, are substituted with perfluoroalkyl groups. However, 1,2-dihydroheterocyclic compounds such as  $\alpha$ -pyrone or  $\alpha$ -pyridone derivatives are easily photoisomerized to bicyclic Dewar isomers, which are useful for the synthesis of cyclobutadienes. The photochemistry of 1,2-dihydroheterocyclic compounds will be discussed, followed by those of fully aromatic compounds.

<sup>6,2</sup> D. H. R. Barton, E. Buschmann, J. Häusler, C. W. Holzaphel, T. Sheradsky, and D. A. Taylor, *J. C. S. Perkin I*, 1107 (1977).

<sup>6,3</sup> K. E. Wilzbach and D. I. Rausch, *J. Am. Chem. Soc.* **92**, 2178 (1970).

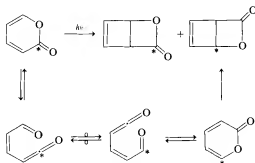
A. PHOTOREACTIONS OF  $\alpha$ -PYRONES

The photoisomer of  $\alpha$ -pyrone was synthesized in order to prepare a cyclobutadiene.<sup>64</sup> It was pyrophoric in air at room temperature and its mass spectrum was similar to that of furan. Flash thermolysis was reported to give many compounds, as shown in Scheme 26.<sup>65</sup> No evidence for the formation of cyclobutadiene was obtained, but carbon dioxide and acetylene products seem to support its intervention.



SCHEME 26

A more detailed study of the photoreaction of  $\alpha$ -pyrone using  $^{13}\text{C}$  labeling showed that the photoreaction was more complex than expected (Scheme 27).<sup>66</sup>



SCHEME 27

The synthesis of cyclobutadiene was accomplished in a matrix of argon (Scheme 28).<sup>67-69</sup> The IR spectrum of cyclobutadiene suggests a square

<sup>64</sup> E. J. Corey and J. Streith, *J. Am. Chem. Soc.* **86**, 950 (1964).

<sup>65</sup> E. Hedaya, R. D. Miller, D. W. McNeil, P. F. D'Angero, and P. Schissel, *J. Am. Chem. Soc.* **91**, 1875 (1969).

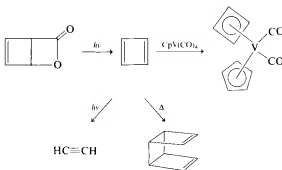
<sup>66</sup> B.-S. Huang, R. G. S. Pong, J. Laurenti, and A. Krantz, *J. Am. Chem. Soc.* **99**, 4154 (1977).

<sup>67</sup> C. Y. Lin and A. Krantz, *J. C. S. Chem. Commun.*, 1111 (1972).

<sup>68</sup> O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 614 (1973).

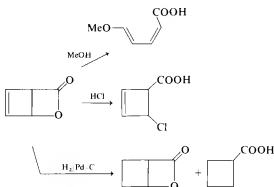
<sup>69</sup> G. Maier, H. G. Hartan, and T. Sayrac, *Angew. Chem.* **88**, 252 (1976).

planar structure which could be photolyzed to acetylene, thermolyzed to a dimer, and converted to a metal complex.<sup>70</sup>



SCHEME 28

Other reactions of the 2-oxabicyclo[2.2.0]hex-5-en-3-one are shown in Scheme 29.<sup>64,71</sup>



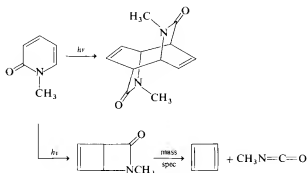
SCHEME 29

### B. PHOTOREACTIONS OF $\alpha$ -PYRIDONES

Photoreaction of  $\alpha$ -pyridones give [2 + 2] dimers. The photolysis of *N*-methyl- $\alpha$ -pyridone in a dilute solution gives a bicyclic isomer, which has a mass spectrum showing  $m/e$  52, perhaps due to cyclobutadiene (Scheme 30).<sup>64</sup>

<sup>70</sup> M. D. Rausch and A. V. Grossi, *J. C. S. Chem. Commun.*, 401 (1978).

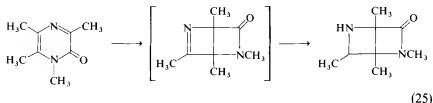
<sup>71</sup> W. H. Pirkle and L. H. McKendry, *J. Am. Chem. Soc.*, **91**, 1179 (1969).



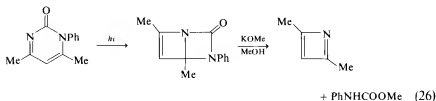
SCHEME 30

There are many reports concerning the product ratio of the dimers and the bicyclic isomer, the solvent effect, and the substituent effect, among others.<sup>72</sup>

Similar reactions of heterocyclic lactams with two heteroatoms have been reported. A pyrazinone gave a bicyclic isomer which was hydrogenated to a diazabicyclohexanone (Eq. 25).<sup>73</sup>



The photolysis of a pyrimidone also gave a bicyclic isomer, which was cleaved with potassium methoxide to an azacyclobutadiene (Eq. 26).<sup>74,75</sup>



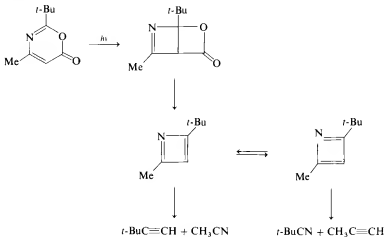
<sup>72</sup> W. L. Dilling, N. B. Terfertiller, and A. B. Mitchell, *Mol. Photochem.* **5**, 371 (1973), and references therein.

<sup>73</sup> H. Furrer, *Chem. Ber.* **105**, 2780 (1972).

<sup>74</sup> T. Nishio, A. Katoh, Y. Omote, and C. Kashima, *Tetrahedron Lett.*, 1543 (1978).

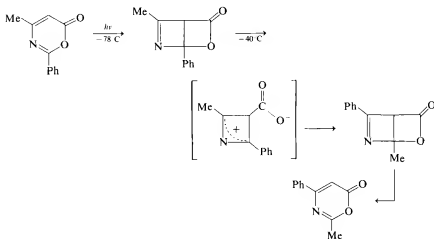
<sup>75</sup> T. Nishio, A. Katoh, C. Kashima, and Y. Omote, *J. C. S. Perkin I*, 607 (1980).

An oxazolone compound is a good precursor of an azacyclobutadiene (Scheme 31).<sup>76</sup>



SCHEME 31

Another isomerization of an oxazolone occurred through bicyclic intermediates (Scheme 32).<sup>77</sup>



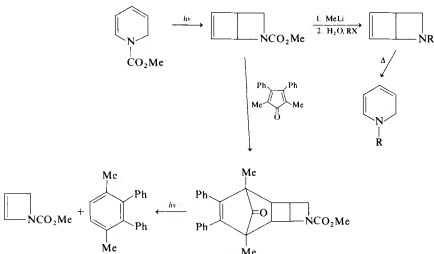
SCHEME 32

<sup>76</sup> G. Maier and U. Schäfer, *Tetrahedron Lett.*, 1053 (1977).

<sup>77</sup> P. DeMayo, A. C. Weedon, and R. W. Zapel, *J. C. S. Chem. Commun.*, 881 (1980).

## C. PHOTOREACTIONS OF 1,2-DIHYDROPYRIDINES

The photoreaction of 1-methoxycarbonyl-1,2-dihydropyridine gave a 2-azabicyclo[2.2.0]hex-5-ene compound,<sup>78</sup> which was useful for the syntheses of N-substituted dihydropyridines.<sup>79</sup> The latter showed peculiar transformations (Scheme 33).<sup>80</sup> The bicyclic intermediate reacted with a cyclopentadienone. The product is a good precursor of azacyclobutene.<sup>81</sup> The advantages of these syntheses are that a 2-azabicyclo[2.2.0]hex-5-ene is more stable and easier to deal with than the corresponding 1,2-dihydropyridine.<sup>82</sup>



SCHEME 33

## D. PHOTOREACTIONS OF PYRYLIUM SALTS

The photoreaction of a substituted pyrylium salt yields an intermediate which is postulated to have a benzvalene and not a Dewar form. A walk

<sup>78</sup> F. W. Fowler, *J. Org. Chem.* **37**, 1321 (1972).

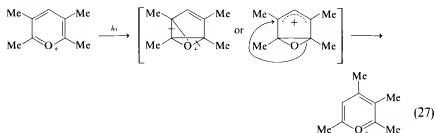
<sup>79</sup> J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, and F. W. Fowler, *J. Am. Chem. Soc.* **98**, 2344 (1976).

<sup>80</sup> I. Hasan and F. W. Fowler, *J. Am. Chem. Soc.* **100**, 6696 (1978).

<sup>81</sup> R. N. Warrenner, G. Kretschmer, and M. N. Paddon-row, *J. C. S. Chem. Commun.*, 806 (1977).

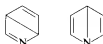
<sup>82</sup> P. Becken, J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, K. A. Zollo, and F. W. Fowler, *J. Am. Chem. Soc.* **101**, 6677 (1979).

mechanism of a 6-oxabicyclo[3.1.0]hexenium ion is not to be neglected (Eq. 27).<sup>83</sup>

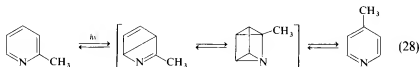


### E. DEWAR PYRIDINES

The studies on Dewar pyridines started recently. Molecular orbital calculations show that the 2,5-bonded Dewar pyridine is more stable than the 1,4-bonded one.<sup>84,85</sup>



The photoisomerization of  $\alpha$ -picoline to  $\gamma$ -picoline in the gas phase is considered to pass through a 2,5-bonded Dewar compound followed by the formation of an azaprismane derivative (Eq. 28).<sup>86</sup>



The photoreaction of pyridine in cyclohexane gives a product which seems to be formed through a Dewar intermediate (Scheme 34).<sup>87</sup>

<sup>83</sup> J. A. Barltrop, A. W. Baxter, A. C. Day, and E. Irving, *J. C. S. Chem. Commun.*, 606 (1980).

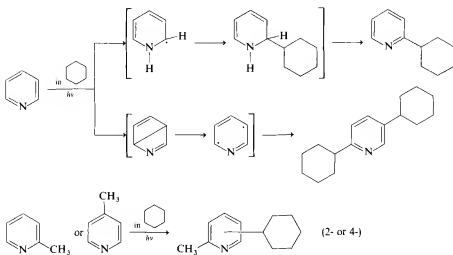
<sup>84</sup> Z. Latajka, H. Ratajczak, W. J. Oville-Thomas, and E. Ratajczak, *J. Mol. Struct.* **21**, 299 (1974).

<sup>85</sup> M. J. S. Dewar, G. P. Ford, J. P. Ritchie, and H. S. Rzepa, *J. Chem. Res., Synop.*, 26 (1978).

<sup>86</sup> S. Caplain and A. Lablache-Combiér, *J. C. S. Chem. Commun.*, 1247 (1970).

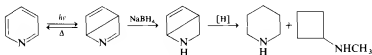
<sup>87</sup> S. Caplain, J. P. Catteau, and A. Lablache-Combiér, *J. C. S. Chem. Commun.*, 1475 (1970).





SCHEME 34

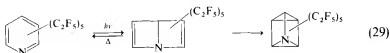
Photolysis of pyridine in acetonitrile causes a decrease in UV absorption, which is restored in the dark (half-life at 25°C was 2.5 min). The same reaction in water in the presence of sodium borohydride gives 2-azabicyclo[2.2.0]hex-5-ene, which can be further reduced to piperidine and *N*-methylcyclobutylamine. These results provided good evidence for Dewar pyridine (Scheme 35).<sup>63</sup>



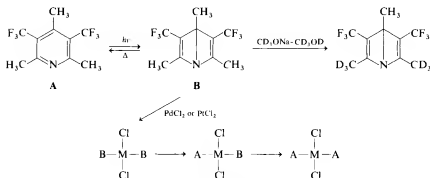
SCHEME 35

These results on unsubstituted or methylated pyridines are consistent with the results of calculations which show that 2,5-bonded Dewar pyridine is more stable. Interestingly, the photoreaction of pentakis(pentafluoroethyl)pyridine gives a 1,4-bonded Dewar pyridine, which is quite stable at room temperature but is in equilibrium with the starting material at 160°C. This Dewar compound seems to be too stable to investigate its reactivity! It converts to an azaprismane by irradiation with high energy UV light (Eq. 29).<sup>88</sup>

<sup>88</sup> M. G. Barlow, J. G. Dingwall, and R. N. Haszeldine, *J. C. S. Chem. Commun.*, 1580 (1970); *J. C. S. Perkin I*, 1542 (1973).



Similarly, a 1,4-bonded Dewar pyridine was obtained in the photolysis of 2,4,6-trimethyl-3,5-bis(trifluoromethyl)pyridine. This Dewar pyridine is much less stable than the pentakis(pentafluoroethyl) counterpart. Thus, while it could be kept in a refrigerator for a few years, it isomerized to the aromatic counterpart on thermolysis. Treatment with sodium methoxide in deuteriomethanol resulted in the deuterium exchange in the  $\alpha$ -methyl but not in the  $\gamma$ -methyl group, suggesting that the stability of this Dewar pyridine is partly due to the pull-push interaction between the trifluoromethyl and the methyl groups on the double bond. Isomerization to the pyridine was catalyzed by acids and transition metals such as Fe or Rh. Complexes with Pd(II) or Pt(II) were isolated and determined to be square planar with a trans-N- $\sigma$  bond as indicated by X-ray analysis. The Dewar pyridine when coordinated as ligands on the metal isomerized to the aromatic form much faster than when noncoordinated (Scheme 36).<sup>89,90</sup> Isomerization was



SCHEME 36

investigated kinetically, and found to be a concerted reaction.<sup>91</sup>

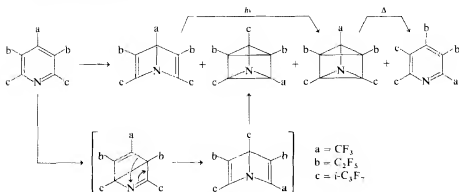
The two examples just considered seem to suggest that the photoreaction of perfluoroalkylated pyridines would give the 1,4-bonded Dewar isomers. However, the photoreaction of 2,6-bis(heptafluoroisopropyl)-3,5-bis(pentafluoroethyl)-4-trifluoromethylpyridine gave a product whose structure

<sup>89</sup> Y. Kobayashi, A. Ohsawa, and Y. Iitaka, *Tetrahedron Lett.*, 2643 (1973).

<sup>90</sup> Y. Kobayashi, A. Ohsawa, M. Baba, T. Sato, and I. Kumadaki, *Chem. Pharm. Bull.* **24**, 2219 (1976).

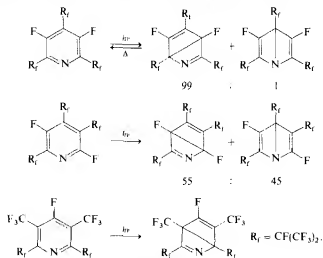
<sup>91</sup> Y. Kobayashi and A. Ohsawa, *Chem. Pharm. Bull.* **24**, 2225 (1976).

suggested the intervention of a 2,5- and a 1,4-bonded Dewar pyridine intermediate (Scheme 37).<sup>92,93</sup>



SCHEME 37

This reaction suggests that isolation of a 1,4-bonded Dewar pyridine does not necessarily mean that it is the primary product. If substituents a and b are the same, as in the previous cases, the products from stepwise rearrangement cannot be distinguished from nonrearranged ones. The first isolation of the stable 2,5-bonded Dewar pyridine was accomplished by the photo-



SCHEME 38

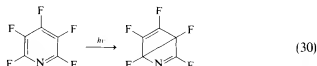
<sup>92</sup> R. D. Chambers, R. Middleton, and R. P. Corbally, *J. C. S. Chem. Commun.*, 731 (1975).

<sup>93</sup> R. D. Chambers and R. Middleton, *J. C. S. Perkin I*, 1500 (1977).

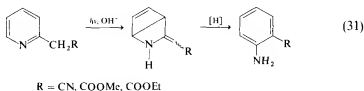
reaction of heptafluoroisopropylated pyridines in the gas phase (see Scheme 38).<sup>94</sup>

These examples show that the 2,5-bonded Dewar pyridine can be formed even if it is substituted with perfluoroalkyl groups. In the second example in Scheme 38 another 2,5-bonded isomer was not formed. This fact shows that a steric effect is important.

The photolysis of perfluoropyridine was reported to give a 2,5-bonded Dewar isomer (Eq. 30).<sup>95</sup>

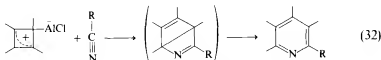


Another 2,5-bonded isomer was used for the synthesis of aniline derivatives (Eq. 31).<sup>96</sup>



In this reaction, the double bond was rearranged to the exo position, which then underwent a formal (3,3) sigmatropic reaction, but this step may be a radical reaction.

The complex of a cyclobutadiene with aluminum chloride reacted with nitriles to give pyridine derivatives, where the intermediates must be Dewar pyridines (Eq. 32).<sup>97</sup>



The mass spectra of cyanopyridines which were isotopically labeled showed that they isomerize to one another, probably through Dewar intermediates (Scheme 39).<sup>98</sup>

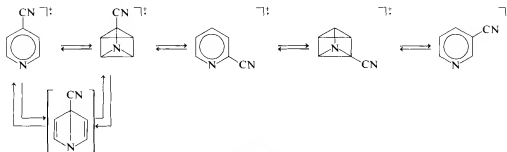
<sup>94</sup> R. D. Chambers and R. Middleton, *J. C. S. Chem. Commun.*, 154 (1977).

<sup>95</sup> E. Ratajczak and B. Sztuba, *J. Photochem.* **13**, 233 (1980).

<sup>96</sup> Y. Ogata and K. Takagi, *J. Org. Chem.* **43**, 944 (1978).

<sup>97</sup> P. B. J. Driessen and H. Hogeveen, *J. Organomet. Chem.* **156**, 265 (1978).

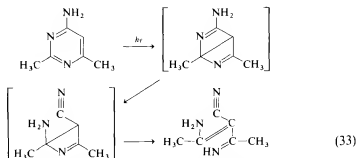
<sup>98</sup> T. A. Molenaar-Langeveld, N. P. E. Vermeulen, N. M. M. Nibbering, R. P. Morgan, A. G. Brenton, J. H. Beynon, D. K. Sen Sharma, and K. R. Jennings, *Org. Mass Spectrom.* **14**, 524 (1979).



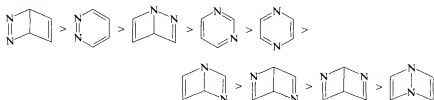
SCHEME 39

## F. DEWAR ISOMERS OF DIAZINES

A Dewar pyrimidine had been formerly postulated to be an intermediate in photoisomerization (Eq. 33),<sup>99</sup> but isolation of a Dewar diazine succeeded much later.



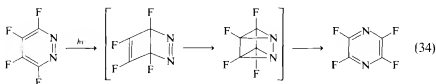
The results of calculations of the energy minima of diazines and their Dewar isomers by the CNDO/2 method show the following order of stabilities:<sup>100</sup>



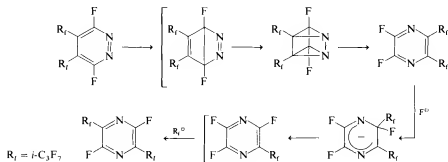
<sup>99</sup> K. L. Wierzchowski, D. Shuger, and A. R. Katritzky, *J. Am. Chem. Soc.*, **85**, 827 (1963).

<sup>100</sup> Z. Latajka, H. Ratajczak, W. J. Orville-Thomas, and E. Ratajczak, *J. Mol. Struct.* **28**, 323 (1975).

Peculiarly, the 3,6-bonded Dewar pyridazine appears to be more stable than pyridazine. This conclusion could originate from the large approximations and the difference in the structure between the aromatic and the Dewar forms. Thus, the order in the Dewar isomers of one diazine might be correct. The photochemical and thermal isomerization of perfluoroalkylated diazines have been investigated mainly by Chamber's group, and Dewar intermediates were proposed for photoisomerizations. The photoisomerization of tetrafluoropyridazine to the pyrazine was given a mechanism shown in Eq. (34).<sup>101</sup>



The rearrangement of 4,5-disubstituted pyridazine to a 2,5-disubstituted pyrazine was postulated to follow a similar mechanism, rearrangement of a perfluoroalkyl group taking place by an addition-elimination mechanism (Scheme 40).<sup>102</sup>



SCHEME 40

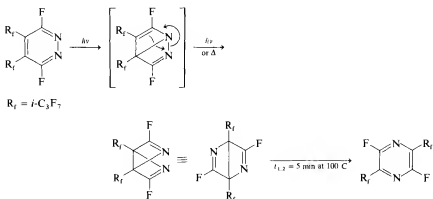
However, more detailed study of the products showed that perfluoro-1,4-di-isopropyl-2,5-diazabicyclo[2.2.0]hexa-2,5-diene was formed (Scheme 41).<sup>103</sup> This result excluded the mechanism in Scheme 40. A similar isomerization of perfluoro-3,6-methylpyridazine to the 2,5-substituted pyrazine was reported.<sup>104</sup>

<sup>101</sup> C. G. Allison, R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *J. C. S. Chem. Commun.*, 1200 (1969).

<sup>102</sup> R. D. Chambers, W. K. R. Musgrave, and K. C. Srivastava, *J. C. S. Chem. Commun.*, 264 (1971).

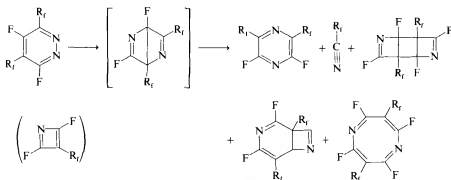
<sup>103</sup> R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J. C. S. Perkin I*, 1130 (1975).

<sup>104</sup> M. G. Barlow, R. N. Haszeldine, and J. A. Pickett, *J. C. S. Perkin I*, 378 (1978).



SCHEME 41

Irradiation of perfluoro-3,5-diisopropylpyridazine gave many products which were derived from an azacyclobutadiene (Scheme 42).<sup>105</sup>



SCHEME 42

The thermolysis of perfluoroalkylpyridazines gives perfluoroalkylpyrimidines and pyrazines through diazabenzvalene intermediates, but not a Dewar isomer.<sup>106</sup>

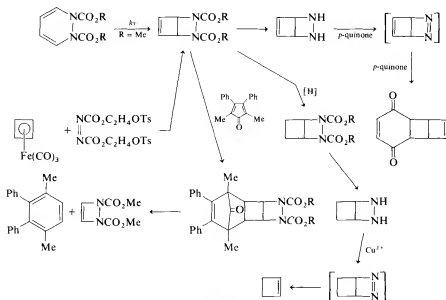
The bicyclic isomer of 1,2-dihydropyridazine-1,2-dicarboxylate was obtained by photolysis.<sup>107</sup> It could be a precursor for cyclobutadiene; it

<sup>105</sup> R. D. Chambers and J. R. Maslakiewicz, *J. C. S. Chem. Commun.*, 1005 (1976).

<sup>106</sup> R. D. Chambers, W. K. R. Musgrave, and C. R. Sargent, *J. C. S. Perkin I*, 1071 (1981), and references therein.

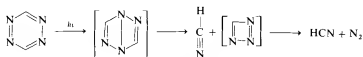
<sup>107</sup> L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *J. C. S. Chem. Commun.*, 686 (1968).

even was synthesized from the latter.<sup>108</sup> The bicyclic material was converted to diazacyclobutenedicarboxylate,<sup>109</sup> and to cyclobutene<sup>110</sup> by separate routes, (Scheme 43). Although 1,2-diazacyclobut-3-enedicarboxylate has six  $\pi$  electrons it does not show any aromaticity.



SCHEME 43

The photoreaction of 1,2,4,5-tetrazine seems to occur through a Dewar intermediate (Scheme 44).<sup>111</sup>



SCHEME 44

<sup>108</sup> S. Masamune, N. Nakamura, and J. Sapadaro, *J. Am. Chem. Soc.* **97**, 918 (1975).

<sup>109</sup> E. E. Nun and R. N. Warren, *J. C. S. Chem. Commun.*, 818 (1972); *Aust. J. Chem.* **32**, 2659 (1979).

<sup>110</sup> E. A. Wildi and B. K. Carpenter, *Tetrahedron Lett.*, 2469 (1978).

<sup>111</sup> R. M. Hochstrasser and A. B. Smith, III, *J. Am. Chem. Soc.* **99**, 271 (1977).



## V. Concluding Remarks

There are only a few examples of Dewar isomers of aromatic compounds defined in a classical sense: nonionic six  $\pi$  electron systems. Therefore, this review includes some mesoionic, tautomeric, and even dihydro aromatic compounds. As shown, this field of chemistry is rather "young"; it will develop further in both synthetic and theoretical aspects.

## Cyclizations under Vilsmeier Conditions

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University of Salford, Salford, England*

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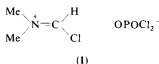
## I. Introduction

The Vilsmeier (or Vilsmeier-Haack or Vilsmeier-Haack-Arnold) reaction is primarily a mild method for formylating a wide variety of substrates.<sup>1</sup> It has limited application to higher acylation and involves the reaction of a Vilsmeier reagent derived from a tertiary amide and an acid chloride (or occasionally a bromide). The most commonly employed amide is *N,N*-dimethylformamide (DMF) and the acid chloride is generally phosphoryl chloride, though phosgene and thionyl chloride are also employed.

<sup>1</sup> For an excellent recent review, see C. Jutz, *Adv. Org. Chem.* **9** (1), 225 (1976).

Solvents are commonly dimethylformamide, a chloroalkane or chloroalkene (methylene chloride, chloroform, 1,2-dichloroethane, etc.) or phosphoryl chloride. Temperatures used are generally in the range 0–100 C.<sup>1a</sup> Substrates include activated aromatic or heteroaromatic compounds, alkenes (including enamines and enol derivatives), methyl or methylene ketones and "active" methyl or methylene groups in general, and hydrazones, azines and aliphatic diazo compounds.

The Vilsmeier reagent (VR) derived from dimethylformamide and phosphoryl chloride has been convincingly shown to have structure **1**<sup>2</sup> despite much debate. Erroneous structures are still reported.<sup>3</sup>



The first reports of such acylations in 1886 involved benzoylation of *N,N*-dialkylanilines with benzanilide in phosphoryl chloride.<sup>4</sup> Dimroth in 1906 noted that resorcinol could be formylated with formanilide in phosphoryl chloride.<sup>5</sup> However, it was not until 1925 when Fischer, Müller, and Vilsmeier reinvestigated<sup>6</sup> the structure of a red dye derived from *N*-methylacetanilide and phosphoryl chloride (Scheme 1) that the acylating role of tertiary amides was fully appreciated and exploited further by Vilsmeier and Haack using *N*-methylformanilide.<sup>7</sup> Thus the first example actually observed involved a cyclization yielding a quinoline. However, although the formylation reaction was rapidly developed, the use of the Vilsmeier reagent for cyclization lay dormant until recently. Most of the data is scattered throughout the chemical literature and the results were frequently unexpected. This

<sup>1a</sup> In our experience many reactions are critically dependent upon the proper choice of solvent and temperature and DMF is not generally the best solvent though it is the commonest. 70–80° C is a good general working temperature.

<sup>2</sup> See Ref. 1 and G. A. Olah and S. J. Kuhn, in "Friedel-Crafts and Related Reactions" (G. A. Olah, ed.), Vol. 3, Part 2, p. 1211. Wiley (Interscience), New York, 1964; H. Ulrich, "The Chemistry of Imidoyl Halides," pp. 87–96. Plenum, New York, 1968.

<sup>2a</sup> Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.* **27**, 2886 (1962); R. M. Silverstein, E. E. Ryskiewicz, C. Willard, and R. C. Koehler, *J. Org. Chem.* **20**, 668 (1955); E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.* **75**, 989 (1953).

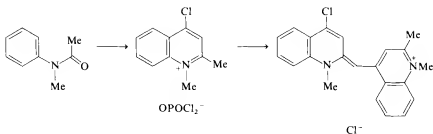
<sup>3</sup> W. Scheuermann, G. McGillivray, and J. White, *Proc. Int. Conf. Raman Spectrosc.*, **5th**, 1976, 68 (1976) [*CA* **88**, 104221f (1978)].

<sup>4</sup> Farbwerker-Hoechst, German Patents 41,751 and 44,077 (1887).

<sup>5</sup> O. Dimroth and R. Zoeppritz, *Ber. Dtsch. Chem. Ges.* **35**, 993 (1902).

<sup>6</sup> O. Fischer, A. Müller, and A. Vilsmeier, *J. Prakt. Chem.* **109**, 69 (1925); cf. M. C. Friedel, *Bull. Soc. Chim. Fr.* **11**, 1028 (1896).

<sup>7</sup> A. Vilsmeier and A. Haack, *Ber. Dtsch. Chem. Ges. B* **60**, 119 (1927).



SCHEME 1

review is an endeavour to correlate this information and demonstrate the powerful potential in synthesis of the underlying principles.

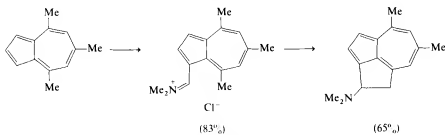
The material is organized according to the size of the ring produced and in order of increasing number of heteroatoms as in the Ring Index.<sup>8</sup> The preparation of carbocyclic ring is included for completeness.

## II. Ring Formation

### A. FIVE-MEMBERED RINGS

#### 1. C<sub>5</sub> Systems

Formylation of 4,6,8-trimethylazulene occurs at the 1-position and the isolated imminium salt is readily cyclized with base (Scheme 2).<sup>9</sup> Ring-activated styrenes such as **2** undergo side-chain formylation with subsequent

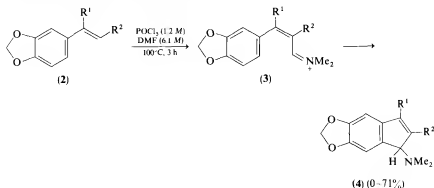


SCHEME 2

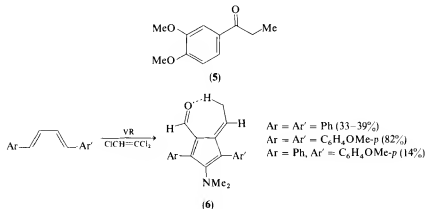
<sup>8</sup> A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed. Am. Chem. Soc., Washington, D.C., 1960.

<sup>9</sup> K. Hafner and J. Schneider, *Justus Liebigs Ann. Chem.* **624**, 37 (1959).

ring closure to give the aminoindenes (**4**). The intermediate (*Z*)-cinnamaldehyde (derived from **3**) could be isolated by reaction at room temperature.<sup>10,10a</sup> Propioveratrone (**5**) under similar conditions gives an indene (**4**;  $R^1 = \text{Cl}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{OMe}$ ) in 75% yield.<sup>11</sup> 1,4-Diarylbutadienes undergo triformylation giving the fulvenes (**6**), the best yields deriving from the most activated analogs (Scheme 3).<sup>12</sup>



$R^1 = \text{H}$ ,  $R^2 = \text{Me}$ , *n*-Pr, *n*-Bu, or Ph



SCHEME 3

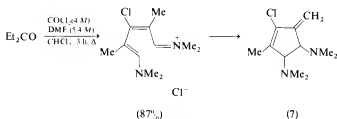
Diethyl ketone is readily diformylated and the derived iminium salt<sup>1</sup> can be cyclized with a variety of reagents giving the dihydrofulvenes (**7**) or deriv-

<sup>10</sup> D. T. Witiak, D. R. Williams, and S. V. Kakodkar, *J. Org. Chem.* **39**, 1242 (1974).

<sup>10a</sup> F. Dallacker, R. D. Maier, R. Morcinek, A. Rabie, and R. van Loo, *Chem. Ber.* **113**, 1320 (1980).

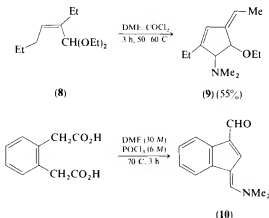
<sup>11</sup> K. Bodendorf and R. Mayer, *Chem. Ber.* **98**, 3565 (1965).

<sup>12</sup> C. Jutz and R. Heinicke, *Chem. Ber.* **102**, 623 (1969).



SCHEME 4

atives thereof (Scheme 4).<sup>13</sup> Unsaturated acetal **8** similarly gives dihydrofulvene **9**, cyclization proceeding under the formylation conditions. A low yield route to a benzofulvene (**10**) has also been noted (Scheme 5).<sup>14</sup>



SCHEME 5

## 2. $C_4N$ Systems

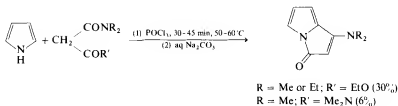
Pyrrole reacts with malonamides in phosphoryl chloride giving pyrrolizines in moderate yields (Scheme 6).<sup>15</sup> Benzimidazole-2-propionic acid undergoes cyclization and subsequent formylation under Vilsmeier conditions at room temperature (RT) (Scheme 7).<sup>16</sup>

<sup>13</sup> J. Zemlicka and Z. Arnold, *Collect. Czech. Chem. Commun.* **26**, 2852 (1961).

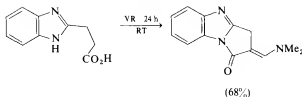
<sup>14</sup> Z. Arnold, *Collect. Czech. Chem. Commun.* **30**, 2783 (1965).

<sup>15</sup> A. Ermili, A. J. Castro, and P. A. Westfall, *J. Org. Chem.* **30**, 339 (1965); W. C. Antony, *ibid.* **25**, 2049 (1960).

<sup>16</sup> H. A. Naik, V. Purnaprajna, and S. Seshadri, *Indian J. Chem., Sect. B* **15B**, 338 (1977).

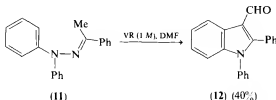


SCHEME 6



SCHEME 7

Hydrazone **11** is claimed to yield formyl indole (**12**)<sup>16a</sup> by Fischer cyclization followed by formylation.<sup>17</sup>



Methyl groups activated by being  $\alpha$  or  $\gamma$  to an annular nitrogen in an *N*-heteroaromatic system can be readily diformylated.<sup>1</sup> When an amino substituent is ortho to the methyl group, cyclization can ensue giving a fused pyrrole (Scheme 8).<sup>18-20</sup> *o*-Methylamino groups result in *N*-methylpyrrole (41%) analogues.<sup>19</sup>

In a related manner the active 5-methyl group of the 6-azaindolizine **13** can be diformylated and the product cyclized *in situ* to the reactive pyrrolic position to give cyclazine **14**.<sup>21</sup>

<sup>16a</sup> The original paper, probably erroneously, suggested that the product was the 4-formyl derivative [see Ref. 1 for further comment (p 323)].

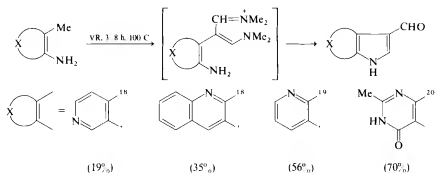
<sup>17</sup> M. A. Kira, Z. M. Nofal, and K. Z. Gadalla, *Tetrahedron Lett.*, 4215 (1970).

<sup>18</sup> B. A. J. Clark, J. Parrick, P. J. West, and A. H. Kelly, *J. Chem. Soc. C*, 498 (1970).

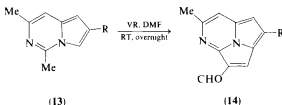
<sup>19</sup> S. Klutchko, H. V. Hansen, and R. I. Meltzer, *J. Org. Chem.* **30**, 3454 (1965).

<sup>20</sup> N. E. Britikova and K. Yu. Novitskii, *Chem. Heterocycl. Comp.* **13**, 1338 (1977) [*CA* **88**, 105263h (1978)]; O. S. Sizova, N. E. Britikova, K. Yu. Novitskii, L. I. Shcherbakova, and G. N. Pershin, *Khim.-Farm. Zh.* **14**, 63 (1980) [*CA* **93**, 239357d (1980)].

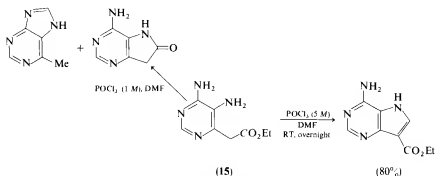
<sup>21</sup> R. Buchan, M. Fraser, and C. Shand, *J. Org. Chem.* **41**, 351 (1976).



SCHEME 8



The product of formylation of the aminopyrimidineacetic ester **15** depends upon the ratio of the reagent used (Scheme 9).<sup>22</sup>



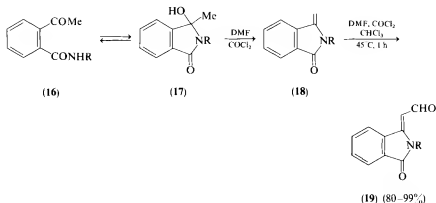
SCHEME 9

2-Acetylbenzamides (**16**) appear to react by way of their cyclic tautomers (**17**) which are dehydrated to the enamides (**18**) and are subsequently formylated (**19**) in high yield.<sup>23</sup>

<sup>22</sup> J. A. Montgomery and K. Hewson, *J. Org. Chem.* **30**, 1528 (1965).

<sup>23</sup> H. R. Muller and M. Seefelder, *Justus Liebigs Ann. Chem.* **728**, 88 (1969).

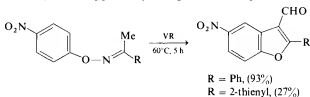




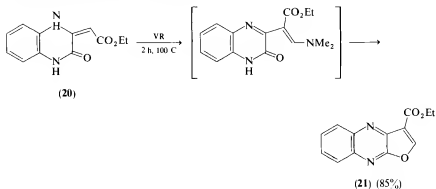
R = alkyl or aryl

### 3. $C_4O$ Systems

Ketoxime *O-p*-nitrophenyl ethers readily undergo Fischer cyclization and formylation, formylation apparently being the first step.<sup>24</sup>



A furanoquinoxaline (21) was unexpectedly obtained on attempted formylation of the quinoxalone (20).<sup>25</sup>

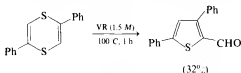


<sup>24</sup> M. A. Kira, M. O. Abdel-Rahman, and Z. M. Nofal, *Egypt. J. Chem.* **19**, 109 (1976).

<sup>25</sup> Y. Kurasawa and A. Takada, *Heterocycles* **14**, 281 (1980).

4.  $C_4S$  Systems

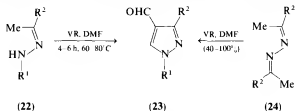
2,5-Diphenyl-1,4-dithiadene is transformed into 3,5-diphenylthiophen-2-aldehyde in a reaction which involves sulfur extrusion (Scheme 10).<sup>26</sup>



SCHEME 10

5.  $C_3N_2$  Systems

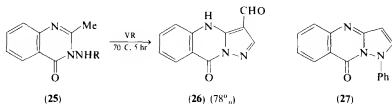
Pyrazoles (**23a-c**) have been generated in high yield by the diformylation of hydrazones (**22a**),<sup>17,27</sup> semicarbazones (**22b**)<sup>28</sup> and azines (**24**).<sup>17</sup>



a:  $R^1$  and  $R^2$  = alkyl or aryl (72–96%)

b:  $R^1$  =  $\text{CONH}_2$ ,  $R^2$  = aryl (54–95%); c:  $R^1$  =  $\text{ArC}=\text{CH}_2$

In a manner related to those described in Scheme 8, 2-methyl-3-aminoquinazolin-4-ones (**25**) are diformylated and cyclized in good yield to the pyrazoloquinazolinones (**26**). The *N*-phenyl derivative (**25**;  $R = \text{Ph}$ ) similarly gave the analog (**27**).<sup>29</sup>



$R = \text{H, Ac or COPh}$

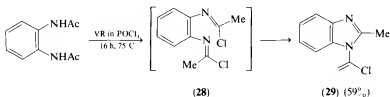
<sup>26</sup> W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.* **76**, 4960 (1954).

<sup>27</sup> M. A. Kira, M. O. Abdel-Rahman, and K. Z. Gadalla, *Tetrahedron Lett.*, 109 (1969).

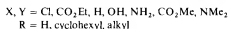
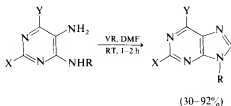
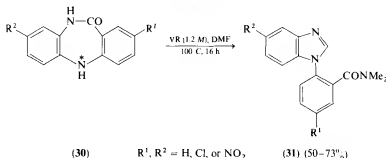
<sup>28</sup> M. A. Kira, M. N. Aboul-Enein, and M. I. Korkor, *J. Heterocycl. Chem.* **7**, 25 (1970).

<sup>29</sup> R. S. Pandit and S. Seshadri, *Indian J. Chem.* **11**, 532 (1973).

Benzimidazole results from the action of Vilsmeier's reagent on *N*-carbethoxy-*o*-phenylenediamine.<sup>30</sup> With *N,N'*-diacetyl-*o*-phenylenediamine and the same reagent, 1-(1-chlorovinyl)-2-methylbenzimidazole (**29**) is produced probably by way of the bischlorovinyl intermediate (**28**) (Scheme 11).<sup>31</sup> The dibenzodiazepines (**30**) have been observed to yield 1-arylbenzimidazoles (**31**) with the same reagents, probably by formylation of the starred nitrogen followed by ring opening and ring closure.<sup>32</sup> Various purines have been made from diaminopyrimidines, generally in good yield (Scheme 12).<sup>33</sup> In an interesting variation, the 6-aminouracils (**32**), which are



SCHEME 11



SCHEME 12

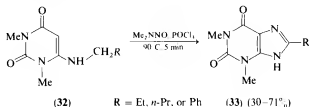
<sup>30</sup> W. Schulze, P. Held, and A. Jumar, *Z. Chem.* **15**, 184 (1975).

<sup>31</sup> O. Meth-Cohn, B. Narine, and B. Tarnowski, *J. C. S. Perkin I*, 1520 (1981).

<sup>32</sup> K. Nagarajan and R. K. Shah, *Indian J. Chem., Sect. B* **14B**, 1 (1976).

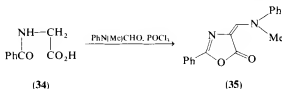
<sup>33</sup> J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958); J. Clark and J. H. Lister, *ibid.*, 5048 (1961); J. H. Lister, *ibid.*, 2228 (1963).

highly reactive in the 5-position to electrophilic substitution, were treated with the "aza-Vilsmeier reagent" derived from *N*-nitrosodimethylamine and phosphoryl chloride, to yield the theophyllines (**33**). The reaction appears to involve ring nitrosation followed by cyclization.<sup>34</sup>

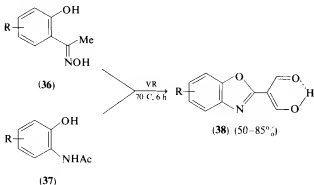


## 6. $\text{C}_3\text{NO}$ Systems

In a manner related to the Erlenmeyer synthesis, hippuric acid (**34**) is converted to the oxazole (**35**) by the action of *N*-methylformanilide and



phosphoryl chloride.<sup>35</sup> 2-Hydroxyacetanilides (**37**) or 2-hydroxyacetophenone oximes (**36**) (which yield the same anilides by Beckmann rearrangement under the reaction conditions) are efficiently transformed into benzoxazoles (**38**). The initially formed 2-methylbenzoxazoles are believed to be



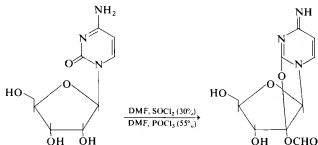
R = H, OH, OMe, Cl, or benzo

<sup>34</sup> F. Yoneda, K. Senga, and S. Nishigaki, *Chem. Pharm. Bull.* **21**, 260 (1973).

<sup>35</sup> J. W. Cornforth, *Heterocycl. Comp.* **5**, 346 (1957).

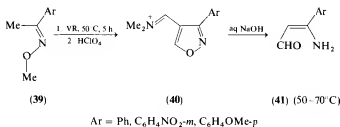
diformylated subsequent to cyclization.<sup>36</sup> These diformyl derivatives are very useful for further ring annelation.<sup>29,36,36a</sup>

Cytidine undergoes cyclization to 2,2'-cyclocytidine under mild Vilsmeier conditions (Scheme 13), phosphoryl chloride being preferred to thionyl chloride.<sup>37</sup>



SCHEME 13

Two isoxazole syntheses are also noted. 3-Phenylisoxazole-4-aldiminium salts (**40**) are derived by initial diformylation of the activated methyl group of acetophenone oxime ethers (**39**) followed by cyclization and precipitation of the perchlorate salt. Attempts to isolate the corresponding isoxazole-4-aldehydes led to ring opening and ultimately the  $\beta$ -aminocinnamaldehydes (**41**) in good yields.<sup>24</sup>



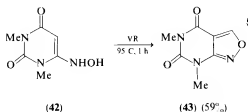
In a manner related to formation of theophyllines (**33**), hydroxyamino-uracil (**42**) is transformed into an isoxazolouracil (**43**).<sup>38</sup>

<sup>36</sup> M. R. Jayanth, H. A. Naik, D. R. Tatke, and S. Seshadri, *Indian J. Chem.*, **11**, 1112 (1973); S. M. Jain and R. A. Pawar, *ibid.*, **13**, 304 (1975); M. R. Chandramohan and S. Seshadri, *ibid.*, **10**, 573 (1972).

<sup>36a</sup> H. V. Hansen, J. A. Caputo, and R. I. Meltzer, *J. Org. Chem.*, **31**, 3845 (1966).

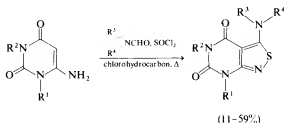
<sup>37</sup> K. Kikugawa and M. Ichino, *Tetrahedron Lett.*, 867 (1970); *J. Org. Chem.*, **37**, 284 (1972).

<sup>38</sup> S. Nishigaki, Y. Kanamori, and K. Senga, *Chem. Pharm. Bull.*, **26**, 2497 (1978).



### 7. $C_3NS$ Systems

A variety of dialkylformamides convert 6-aminouracil to isothiazolouracils in the presence of thionyl chloride (Scheme 14).<sup>39</sup> The sulfur atom is provided by the thionyl chloride.<sup>40</sup>

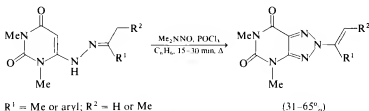


$R^1$ – $R^4$  = alkyl

SCHEME 14

### 8. $C_2N_3$ Systems

In a reaction similar to the formation of theophyllines (**32**  $\rightarrow$  **33**), uracil-6-yl hydrazones are transformed into triazolouracils by the action of *N*-nitrosodimethylamine and phosphoryl chloride in refluxing benzene (Scheme 15).<sup>41</sup>



SCHEME 15

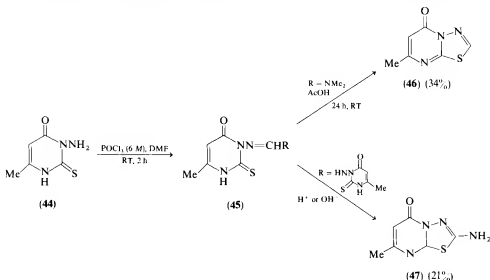
<sup>39</sup> Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull.* **24**, 970 (1976).

<sup>40</sup> J. P. Chupp, D. H. Dahm, and K. L. Leschinsky, *J. Heterocycl. Chem.* **12**, 485 (1975).

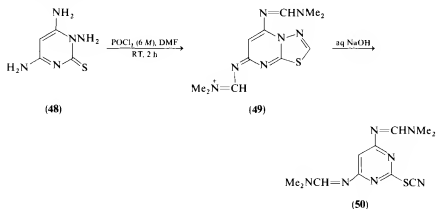
<sup>41</sup> K. Senga, Y. Kanamori, S. Nishigaki, and F. Yoneda, *Chem. Pharm. Bull.* **24**, 1917 (1976).

9.  $C_2N_2S$  Systems

Arylamines often yield formamidines with Vilsmeier reagents. The derived amidines (**45**) of 3-aminopyrimidine-2-thiones (**44**) may be separated and cyclized to give the thiadiazolopyrimidines (**46**) and (**47**).<sup>42</sup> In a similar way



the salts (**49**) may be derived from the 1,4,6-triaminopyrimidine-2-thione (**48**). However, attempts to isolate the free base resulted in formation of the diaminopyrimidine thiocyanate (**50**).<sup>43</sup>



<sup>42</sup> T. Tsuji, *Chem. Pharm. Bull.*, **22**, 471 (1974).

<sup>43</sup> T. Tsuji and Y. Kamo, *Chem. Lett.*, 641 (1972); E. C. Taylor and R. W. Morrison, *J. Org. Chem.*, **32**, 2379 (1967).

## B. SIX-MEMBERED RINGS

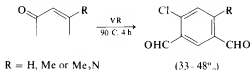
1.  $C_6$  Systems

Several routes to benzaldehydes have been elaborated from 1,3-diketones,  $\alpha,\beta$ -unsaturated diketones or from polyenes. Thus, acetylacetone derivatives (**51**) are useful precursors of 2,4-dichlorobenzaldehydes (**52**) by way of deformylation and cyclization.<sup>44</sup> The best yields are obtained when  $R^1$  is



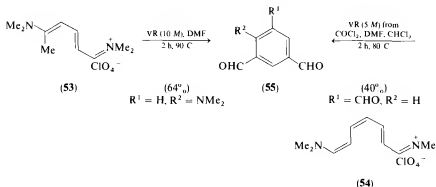
$R^1$  and  $R^2 = H$  or Me

hydrogen. Similarly, methyl propenyl ketones give isophthalaldehydes (Scheme 16) by triformylation and cyclization,<sup>44a</sup> while the salts (**53** and **54**)



SCHEME 16

are sources of the aldehydes (**55**) by deformylation prior to cyclization.<sup>44a</sup>

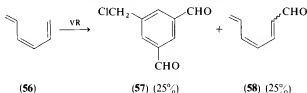


<sup>44</sup> M. Weissenfels, M. Puls, M. Haase, U. Pawlowski, and H.-F. Uhlig, *Z. Chem.* **17**, 56 (1977).

<sup>44a</sup> A. Holy and Z. Arnold, *Collect. Czech. Chem. Commun.* **30**, 53 (1965).



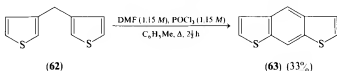
The Vilsmeier method has been used to formylate 1,3,5-hexatrienes (**56**) yielding the aldehydes (**57** and **58**). It seems likely that suitable experimental conditions would make this a viable route to benzaldehydes.<sup>45</sup>



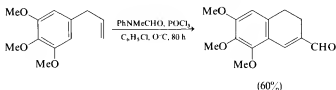
Diformylation and cyclization of the boron trifluoride complex (**59**) of 1-acetyl-2-hydroxynaphthalene surprisingly gave the peri-cyclized, phenalenone (**60**) as the major product, rather than the expected chromone (**61**).<sup>46</sup>



Dithienobenzene (**63**) may be isolated by the Vilsmeier formylation of



3,3'-dithienylmethane (**62**) with concomitant cyclization.<sup>47</sup> In a related reaction, however, with 3,4,5-trimethoxyallylbenzene, a dihydronaphthaldehyde resulted rather than the aromatized analog (Scheme 17).<sup>48</sup> This reaction



SCHEME 17

<sup>45</sup> P. C. Traas, H. J. Takken, and H. Boelens, *Tetrahedron Lett.*, 2129 (1977).

<sup>46</sup> G. A. Reynolds and J. A. Van Allen, *J. Heterocycl. Chem.*, **6**, 375 (1969).

<sup>47</sup> M. Ahmed, J. Ashby, and O. Meth-Cohn, *J. Chem. Soc. D*, 1094 (1970); M. Ahmed, Ph.D. Thesis, University of Salford (1969).

<sup>48</sup> N. S. Narasimhan and T. Mukhopadhyay, *Tetrahedron Lett.*, 1341 (1979).

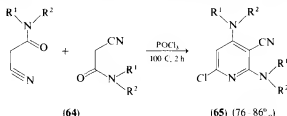
has recently been extended to a variety of analogs.<sup>10a</sup> Labeling data suggested hydrogen transfer from the methyl group of the anilide had occurred.

## 2. *C*<sub>5</sub>*N* Systems

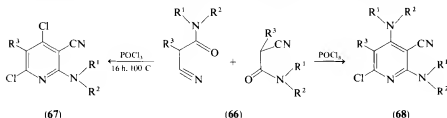
A variety of pyridine ring syntheses stem from Vilsmeier formylation of alkenes, enamines, vinyl ethers, ketones, and related systems followed by a separate cyclization of the derived salts with ammonium chloride or acetate.<sup>49</sup>

A number of dimerizations of amides in hot phosphoryl chloride have been shown to give pyridines.

Thus, two equivalents of *N,N*-dialkylcyanoacetamides (**64**) cyclize to pyridines (**65**) on treatment with hot phosphoryl chloride.<sup>50,50a</sup> When the



cyanoacetamide methylene group is alkyl-substituted (**66**), no dimerization occurs unless this group ( $\text{R}^3$ ) is isopropyl or benzyl, which can leave. The nature of the product depends on the reaction time; prolonged heating gives 4,6-dichloropyridines (**67**) whereas shorter times give a mixture of **67** and **68**.<sup>51</sup> Furthermore, the "unreactive" cyanoacetamides (e.g., **66**;  $\text{R} = \text{Me}$  or



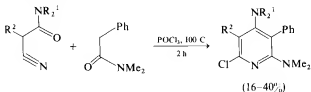
<sup>49</sup> C. Jutz, W. Muller, and E. Muller, *Chem. Ber.* **99**, 2479 (1966); Z. Arnold, *Collect. Czech. Chem. Commun.* **25**, 1308 (1960); *Experientia* **15**, 415 (1959); J. Zemlicka and Z. Arnold, *Collect. Czech. Chem. Commun.* **26**, 2838 (1961); C. Jutz, *Ind. Chem. Belge* **32** (Spec. No. Part III), 127 (1967) [*C.A.* **70**, 67,312s (1969)], Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.* **28**, 2040 (1963); C. Jutz and W. Muller, *Chem. Ber.* **100**, 1536 (1967); P. C. Traas and H. Boelens, *Recl. Trav. Chim. Pays-Bas* **92**, 985 (1973).

<sup>50</sup> A. L. Cossey, R. L. N. Harris, J. L. Huppatz, and J. N. Phillips, *Angew. Chem., Int. Ed. Engl.* **11**, 1098 (1972).

<sup>50a</sup> *Aust. J. Chem.* **29**, 1039 (1976).

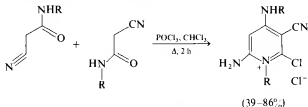
<sup>51</sup> A. L. Cossey, R. L. N. Harris, J. L. Huppatz, and J. N. Phillips, *Angew. Chem., Int. Ed. Engl.* **11**, 1100 (1972).

or Et) may be condensed with other amides to give pyridines under similar conditions (Scheme 18).<sup>51</sup>



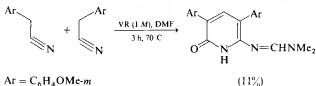
SCHEME 18

Secondary cyanoacetamides dimerize by a different mode and under milder conditions to give pyridinium salts (Scheme 19).<sup>50a,52</sup>



SCHEME 19

Low yields of pyridines, together with numerous other products, result from the attempted formylation of phenylacetonitriles (e.g., Scheme 20).<sup>53</sup>



SCHEME 20

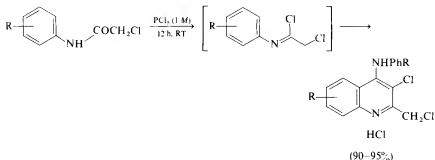
Probably the most important application of the Vilsmeier reaction in ring synthesis derives from the original Vilsmeier quinoline synthesis which was largely unexploited for almost 50 years. Most of the results were unexpected or fortuitous.

von Braun<sup>54</sup> noted that  $\alpha$ -chloroacetanilides dimerize under conditions designed to make the corresponding imidoil chlorides, often in high yields (Scheme 21).

<sup>52</sup> A. L. Cossey, R. L. N. Harris, J. L. Huppatz, and J. N. Phillips, *Angew. Chem., Int. Ed. Engl.* **11**, 1099 (1972).

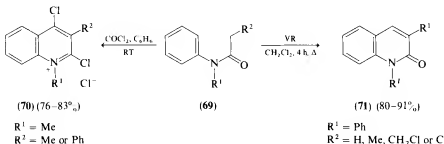
<sup>53</sup> T. Hirota, T. Koyama, T. Nanba, and M. Yamato, *Chem. Pharm. Bull.* **25**, 2838 (1977).

<sup>54</sup> J. van Braun and A. Heymons, *Ber. Dtsch. Chem. Ges. B* **63**, 3191 (1930).



SCHEME 21

*N*-Substituted acetanilides (**69**), the original substrates studied by Vilsmeier (see Scheme 1), are highly reactive compounds for quinoline formation. Thus, quinolinium salts (**70**) derive from the action of phosgene,<sup>55</sup> while 2-quinolones (**71**) are readily formed by Vilsmeier formylation of the same substrates.<sup>56,57</sup> The formylation of *N*-phenylacetanilides (**69**; R<sup>1</sup> = Ph) was initially misinterpreted,<sup>58</sup> but has now been shown to be a highly efficient route to 1-phenyl-2-quinolones.<sup>57</sup>



The reaction of acetanilides (**72**) with Vilsmeier's reagent in POCl<sub>3</sub> is an efficient route to 2-chloroquinoline-3-aldehydes (**73**) by diformylation of the side chain. In those cases where cyclization does not occur efficiently (e.g., R = Cl or Br) the hydrolyzed intermediate (**74**) may be separately cyclized with polyphosphoric acid (PPA) to give the quinolones (**75**).<sup>31,59</sup>

Interestingly, the related acetamidothiophenes (**76**) can be converted to either the chlorothienopyridines (**77**) or the chlorothienopyridine aldehydes

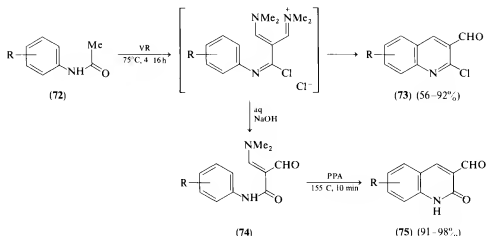
<sup>55</sup> H. Ahlbrecht and C. Vonderheid, *Chem. Ber.* **108**, 2300 (1975).

<sup>56</sup> J. P. Chupp and S. Metz, *J. Heterocycl. Chem.* **16**, 65 (1979).

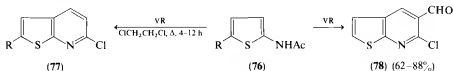
<sup>57</sup> R. Hayes, O. Meth-Cohn, and B. Tarnowski, *J. Chem. Res., Synop.*, 414 (1980); K. E. Schulte and D. Bergenthal, *Arch. Pharm. (Weinheim, Ger.)* **313**, 890 (1980).

<sup>58</sup> K. E. Schulte and D. Bergenthal, *Arch. Pharm. (Weinheim, Ger.)* **312**, 265 (1979).

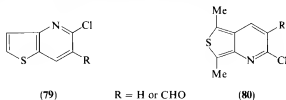
<sup>59</sup> O. Meth-Cohn, B. Narine, and B. Tarnowski, *Tetrahedron Lett.*, 3111 (1979).



R = Me, OMe, Cl, Br, or NO<sub>2</sub>



(78) by proper choice of conditions.<sup>59a,60</sup> These reactions involve ring formylation prior to cyclization and have been extended to the synthesis of the isomers (79 and 80) from 3-acetamido- and 3-acetamido-2,5-dimethylthiophenes,<sup>59a,60</sup> respectively, as well as to the synthesis of a chloroselenothiophene.<sup>60a</sup> Only highly reactive acetanilides (e.g., 3,5-dimethoxyacetanilide) can be made to give chloroquinolines.<sup>59a,60</sup>



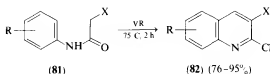
Acylanilides (81; e.g., X = Me, Ph, CH<sub>2</sub>Cl, CH<sub>2</sub>Cl, CH<sub>2</sub>CH<sub>2</sub>Cl) all readily cyclize to 2-chloro-3-substituted quinolines (82) under the same conditions.<sup>61</sup>

<sup>59a</sup> O. Meth-Cohn and B. Narine, *Tetrahedron Lett.*, 2045 (1978).

<sup>60</sup> O. Meth-Cohn, B. Narine, and B. Tarnowski, *J. C. S. Perkin I*, 1531 (1981).

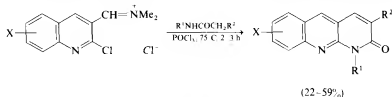
<sup>60a</sup> See also C. Paulmier and F. Outurquin, *J. Chem. Res., Synop.*, 318 (1977); *J. Chem. Res., Miniprint*, 3660 (1977).

<sup>61</sup> O. Meth-Cohn, S. Rhouti, and B. Tarnowski, *Tetrahedron Lett.*, 4885 (1979); O. Meth-Cohn, S. Rhouti, B. Tarnowski, and A. Robinson, *J. C. S. Perkin I*, 1537 (1981).



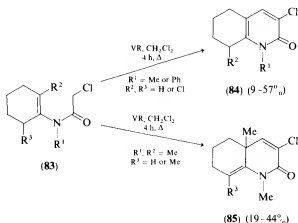
All these quinoline-forming reactions show a remarkable selectivity in that meta-substituted acetanilides invariably yield only 7-substituted quinolines, cyclization taking place para to the substituent.

In a useful extension the reaction mixture from formylation of an acetanilide can be treated with another secondary acylamide in phosphoryl chloride to yield a pyridoquinolone in a one-pot procedure (Scheme 22).<sup>62</sup>



SCHEME 22

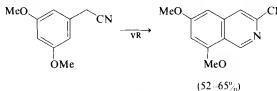
Related cyclizations of enamides have also recently been reported. Thus, the chloroacetylenamides (**83**) give fused pyridines (**84** or **85**), the position of the double bond depending upon the nature of the substituents in the cyclohexene ring.<sup>56</sup>



Isoquinolines are formed by formylation of arylacetoneitriles though often in low yields and with other products. The most successful examples involve

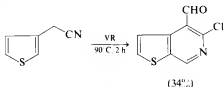
<sup>62</sup> O. Meth-Cohn and B. Tarnowski, *Tetrahedron Lett*, 3721 (1980).

electron-rich ring systems. Thus, 3,5-dimethoxyphenylacetonitrile gives 3-chloro-6,8-dimethoxyisoquinoline on Vilsmeier formylation (Scheme 23).<sup>53,63</sup>



SCHEME 23

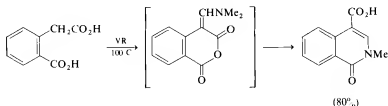
3-Thienylacetonitrile similarly yields a further formylated thienopyridine (Scheme 24).<sup>60a</sup>



SCHEME 24

Homophthalic acid surprisingly yields an isoquinoline upon Vilsmeier formylation, apparently by rearrangement and cyclization of the side-chain formylated intermediate (Scheme 25). This intermediate may be isolated at low temperatures.<sup>64</sup> In a related manner the isoquinolone (**87**) has been synthesized from the toluic acid (**86**).<sup>64a</sup>

The well-known Bischler–Napieralski reaction, in effect an intramolecular Vilsmeier cyclization, is reviewed elsewhere.<sup>65</sup>



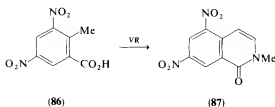
SCHEME 25

<sup>63</sup> T. Koyama, T. Hirota, I. Ito, M. Toda, and M. Yamato, *Yakugaku Zasshi*, **89**, 1492 (1969); T. Koyama, T. Hirota, Y. Shinohara, M. Yamato, and S. Ohmori, *Chem. Pharm. Bull.*, **23**, 497 (1975).

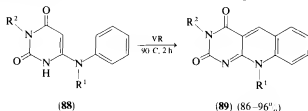
<sup>64</sup> V. H. Belgaukar and R. N. Usgaonkar, *Chem. Ind. (London)*, 954 (1976); *Tetrahedron Lett.*, 3849 (1975).

<sup>64a</sup> V. L. Zbarskii, V. K. Zav'yalova, and E. Y. Orlova, *Tezisy Vses. Simp. Org. Sint. Benzoidnye Aromat. Soedin., Ist.*, 1979, 67 (1974) [*CA* **87**, 22615c (1977)].

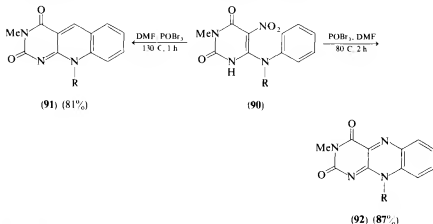
<sup>65</sup> W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 7 (1951).



Pyrimidinoquinolines (89) are efficiently formed by cyclization of 6-arylamino-uracils (88).<sup>66</sup> Ethyl chloroformate can replace the DMF in the



reaction<sup>67</sup> and a number of analogs can be made.<sup>68</sup> When conducted at ambient temperature, the intermediate 5-formylated uracil is isolable.<sup>68a</sup> Using the corresponding 5-nitro-uracils (90) and DMF in phosphoryl bromide at 130°C allows substitution of the nitro group (91), while at 80°C the reductive cyclization of the nitro group occurs (92).<sup>69</sup>



R = alkyl

<sup>66</sup> F. Yoneda and Y. Sakuma, *J. C. S. Chem. Commun.*, 203 (1976); F. Yoneda, Y. Sakuma, S. Mizumoto, and R. Ito, *J. C. S. Perkin I*, 1805 (1976).

<sup>67</sup> K. Ikawa, F. Takami, Y. Fukui, and K. Tokuyama, *Tetrahedron Lett.*, 3279 (1969).

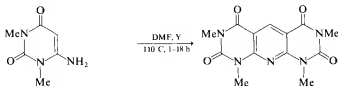
<sup>68</sup> M. Janda and P. Hemmerich, *Angew. Chem., Int. Ed. Engl.* **15**, 443 (1976).

<sup>68a</sup> R. W. Grauert, *Justus Liebigs Ann. Chem.*, 1802 (1979).

<sup>69</sup> Y. Sakuma, Y. Matsushita, and F. Yoneda, *Heterocycles* **9**, 1767 (1978).



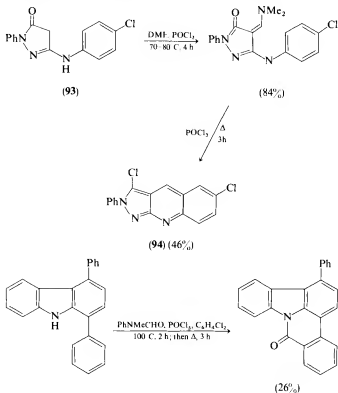
Self-condensation of 6-aminouracils occurs on treatment with DMF and an acid (Scheme 26).<sup>34,70</sup>



Y = H<sub>2</sub>SO<sub>4</sub>, HCl, BF<sub>3</sub>, or Me<sub>2</sub>SO<sub>4</sub>

SCHEME 26

Similarly, arylaminopyrazolone (**93**) may be transformed into a pyrazoloquinoline (**94**) preferably in two steps.<sup>71</sup>



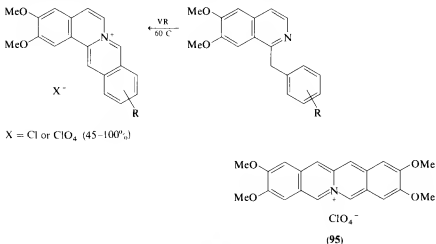
SCHEME 27

<sup>70</sup> H. Brederick, R. Effenberger, and G. Simchen, *Chem. Ber.* **97**, 1403 (1964).

<sup>71</sup> V. Purnaprajna and S. Seshadri, *Indian J. Chem., Sect. B* **14B**, 971 (1976).

The unexpected formation of an indolophenanthridine occurs on attempted formylation of 1,4-diphenylcarbazole (Scheme 27).<sup>72</sup>

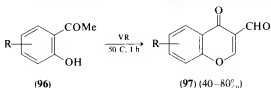
1-Benzylisoquinolines yield berberinium salts on formylation (Scheme 28),<sup>73,73a</sup> as do the corresponding 3,4-dihydro derivatives. The corresponding 3-benzylisoquinolines give, for example, the linear analog (95).<sup>73</sup>



SCHEME 28

### 3. C<sub>5</sub>O Systems

*o*-Hydroxyacetophenones (96) cyclize in good yield to give the valuable intermediates, 3-formylchromones (97).<sup>74,74a</sup> Similar reactions occur with



<sup>72</sup> A. Teitei, *Aust. J. Chem.* **23**, 185 (1970).

<sup>73</sup> W. Wiegand, D. Sasse, H. Reinhart, and L. Faber, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **25B**, 1408 (1970).

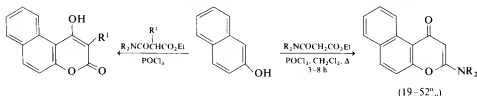
<sup>73a</sup> T. Kametani, M. Takeshita, F. Satoh, and K. Nyu, *Yakugaku Zasshi* **94**, 478 (1974).

<sup>74</sup> H. Harnish, *Ger. Offen.*, 2,122,314 (1972) [*CA* **78**, 59,787a (1973)]; *Justus Liebigs Ann. Chem.* **765**, 8 (1972).

<sup>74a</sup> A. Nohara, T. Umetani, and Y. Sanno, *Tetrahedron Lett.*, 1995 (1973); *Ger. Offen.* 2,317,899 (1973) [*CA* **80**, 14932u (1974)]; *Tetrahedron* **30**, 3553 (1974).

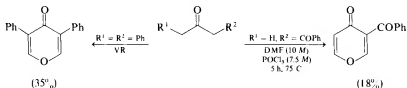
appropriately substituted naphthalenes and coumarins.<sup>74</sup> Furthermore, if the methyl is substituted with, for example, a phenyl group, a 3-phenyl-chromone is produced.<sup>75</sup> The initially diformylated acetophenone can, in the case of less reactive systems, be separately cyclized.<sup>76</sup> Another variation involves conversion of the 2-hydroxyacetophenone to a difluoro-1,3,2-dioxaborin with boron trifluoride and subsequent formylation.<sup>46,77</sup>

An ingenious variation of the Vilsmeier reagent is illustrated in the synthesis of the naphthopyrones with difunctional ester amides (Scheme 29).<sup>78</sup>



SCHEME 29

Monocyclic pyrones are derived by formylation of various simple ketones. Thus, dibenzyl ketone yields 3,5-diphenyl-4-pyrone,<sup>79</sup> while benzoylacetone gives 3-benzoyl-4-pyrone (Scheme 30).<sup>44</sup>



SCHEME 30

#### 4. C<sub>5</sub>S Systems

As in the formation of pyrimidinoquinolines in Section II.B,2 (p. 229), 5-phenyl-thiouracils can be formylated and preferably separately cyclized

<sup>74</sup> S. A. Kagal, P. M. Nair, and K. Venkataraman, *Tetrahedron Lett.*, 593 (1962).

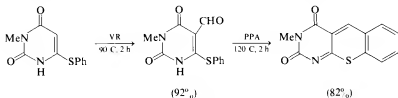
<sup>75</sup> V. M. Vaslov and G. G. Jakobson, *Iz. Akad. Nauk SSSR* **4**, 893 (1969) [*CA* **71**, 30322g (1969)].

<sup>76</sup> D. Kaminsky, S. Klutchko, and M. von Strandtmann, U.S. Patents 3,887,585 (1975) [*CA* **83**, 178,816x (1975)]; 4,008,252 (1977) [*CA* **87**, 5808a (1977)]; D. Kaminsky, U.S. Patents, 3,898,218, 3,879,426 (1975) [*CA* **83**, 79,081x (1975); **84**, 17388q (1976)].

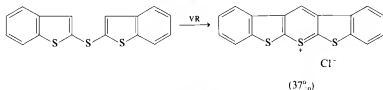
<sup>77</sup> A. Ermili and G. Roma, *Gazz. Chim. Ital.* **101**, 269 (1971); A. Ermili, G. Roma, and A. Balbi, *ibid.*, 651; A. Ermili, G. Roma, M. Mazzei, A. Balbi, A. Cuttica, and N. Passerini, *Farmaco, Ed. Sci.* **29**, 225 (1974); A. Ermili, G. Roma, and F. Braguzzi, *Ann. Chim. (Rome)* **62**, 458 (1972).

<sup>79</sup> M. Weissenfels, M. Pulst, and P. Schneider, *Z. Chem.* **13**, 175 (1973).

to the thio analogs (Scheme 31).<sup>80</sup> Bisbenzothienyl sulfide is cyclized to the corresponding thiopyryllium salt, although this reaction is better conducted with Rieche reagents (e.g.,  $\text{MeOCHCl}_2$  and  $\text{SnCl}_4$ ) (Scheme 32).<sup>47</sup>



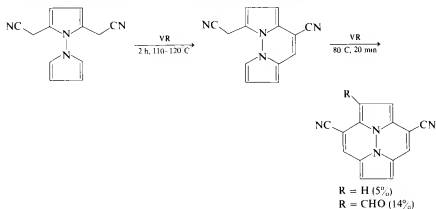
SCHEME 31



SCHEME 32

### 5. $\text{C}_4\text{N}_2$ Systems

In low yield an interesting  $12\pi$  system based on N—N-linked pyrroles has been synthesized by multiple cyclization (Scheme 33).<sup>81</sup>



SCHEME 33

<sup>80</sup> F. Yoneda, M. Kawazoe, and Y. Sakuma, *Tetrahedron Lett.*, 2903 (1978).

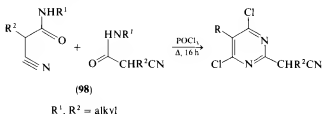
<sup>81</sup> W. Flitsch, H. Lerner, and H. Zimmermann, *Chem. Ber.* **110**, 2765 (1977).

Routes to pyrimidines frequently involve the use of formamide in place of DMF and phosphoryl chloride. Pyrimidine syntheses involving Vilsmeier conditions include the ready acylation of 3-aminoacrylonitriles in good yields (Scheme 34).<sup>82,83</sup> Cyanoacetamides such as **98** tend to dimerize in

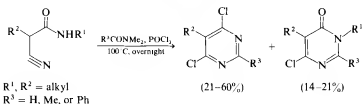


SCHEME 34

phosphoryl chloride solution (Scheme 35).<sup>84</sup> However, in the presence of an added *t*-amide the mixed condensation proceeds well (Scheme 36). Increasing amounts of a pyrimidone by-product arise as the alkyl substituent  $\text{R}^1$  becomes less efficient as a leaving group.<sup>85</sup>



SCHEME 35



SCHEME 36

Alloxazines<sup>34</sup> (**99**) and isalloxazines<sup>86</sup> (**100**) are conveniently derived from 6-arylaminoouracils on treatment with the "aza-Vilsmeier reagent"

<sup>82</sup> R. R. Crenshaw and R. A. Partyka, *J. Heterocycl. Chem.* **7**, 871 (1970).

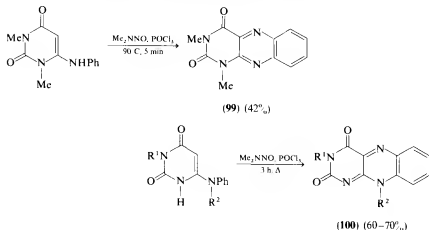
<sup>83</sup> R. L. N. Harris, J. L. Huppertz, and T. Teitel, *Aust. J. Chem.* **32**, 669 (1979).

<sup>84</sup> A. L. Cossey, R. L. N. Harris, J. L. Huppertz, and J. N. Phillips, *Angew. Chem., Int. Ed. Engl.* **13**, 809 (1974).

<sup>85</sup> R. L. N. Harris and J. L. Huppertz, *Angew. Chem., Int. Ed. Engl.* **16**, 779 (1977).

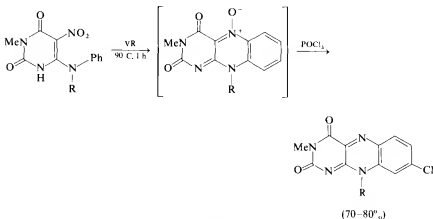
<sup>86</sup> F. Yoneda, K. Shinokawa, Y. Sakuma, and K. Senga, *Heterocycles* **6**, 1179 (1977).

*N*-nitrosodimethylamine and phosphoryl chloride (Scheme 37). The formation of isoalloxazines by the action of phosphoryl bromide and DMF on



SCHEME 37

5-nitro-6-arylaminoouracils appears in **90** → **92**. The corresponding reaction with phosphoryl chloride results in deoxygenation and chlorination (Scheme 38).<sup>87</sup> The presence of a para substituent in the phenylamino ring prevents chlorination.

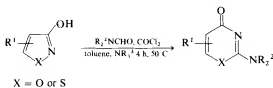


SCHEME 38

<sup>87</sup> F. Yoneda, Y. Sakuma, and K. Shinozuka, *J. C. S. Chem. Commun.*, 681 (1977).

6.  $C_4NO$  and  $C_4NS$  Systems

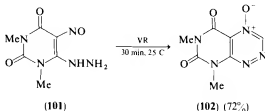
1,3-Oxazin-4-ones and 1,3-thiazin-4-ones are available from 3-hydroxyisoxazoles or 3-hydroxyisothiazoles under Vilsmeier conditions (Scheme 39).<sup>88</sup>



SCHEME 39

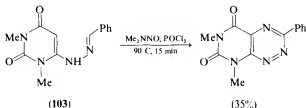
7.  $C_3N_3$  Systems

Two approaches to fervenulins use Vilsmeier conditions. Thus, the 5-nitroso-6-hydrazinouracil (**101**) gives fervenulin-4-oxide (**102**) (Scheme 40)<sup>89</sup>



SCHEME 40

and, using the aza-Vilsmeier reagent, benzylidenehydrazinouracil (**103**) is transformed into a 3-phenylfervenulin (Scheme 41).<sup>41</sup>



SCHEME 41

Undoubtedly, other fascinating applications of the Vilsmeier reaction will be forthcoming.

<sup>88</sup> K. Tomita and T. Murakami, *Jpn. Tokkyo Koho* **20**, 504 (1979) [*CA* **91**, 157,755b (1979)].

<sup>89</sup> M. Ichiba, K. Senga, and S. Nishigaki, *J. Heterocycl. Chem.* **14**, 175 (1977).

## Recent Advances in Furan Chemistry. Part II\*

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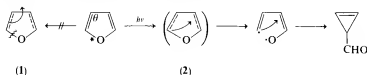
\* Part I of this work appears in *Advances in Heterocyclic Chemistry*, Volume 30.



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## I. Photochemistry

During the period of review, a book containing major sections dealing with the photochemistry of furan and related heterocycles appeared.<sup>1</sup> Although well established, the photochemical ring contraction of furan (Scheme 1) could originate from the ground state as well as it could from



SCHEME 1

the triplet excited state.<sup>2</sup> Calculations reveal that the simple break-twist mechanism indicated in 1 could never operate because the energy barrier is too high; first there must be a distortion consisting of an increase in an internal angle  $\theta$  to about  $122^\circ$  and a lengthening of one C—O bond (starred). The geometry in 2 can then be reached and the crossing of appropriate energy levels becomes feasible.<sup>3</sup>

Originally suggested by Hiraoka,<sup>4</sup> a cyclopropene intermediate is now believed to be present during the photochemical conversion of furans to

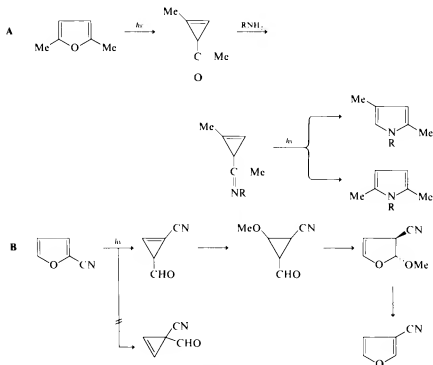
<sup>1</sup> O. Burchardt, ed., "Photochemistry of Heterocyclic Compounds." Wiley, New York, 1976.

<sup>2</sup> L. Salem, W. G. Douglas, and N. J. Turro, *J. Chem. Phys.* **70**, 694 (1971).

<sup>3</sup> E. Poquet, A. Dargelos, and M. Chailet, *Tetrahedron* **32**, 1729 (1976).

<sup>4</sup> H. Hiraoka and R. Srinivasan, *J. Am. Chem. Soc.* **90**, 2720 (1968); R. Srinivasan, *Pure Appl. Chem.* **16**, 65 (1968); H. Hiraoka, *J. Phys. Chem.* **74**, 574 (1970).

pyrroles in the presence of amines (Scheme 2A).<sup>5</sup> It was introduced to account for certain rearrangements, especially that of 2-methylfuran to 3-methylfuran.<sup>4</sup> <sup>6</sup> The cyclopropenes can be trapped by solvent methanol, as shown in Scheme 2B for furan-2-carbonitrile which gives almost exclusively a mixture of stereoisomeric methoxycyclopropanes. When these are heated or chromatographed they lose methanol and are transformed into furan-3-carbonitrile.<sup>6</sup>



SCHEME 2

Thus, furan resembles thiophene rather than pyrrole, which is photochemically converted to a derivative of 5-azabicyclo[2.1.0]pentane; but there are some reactions of furan that are perhaps more easily interpreted in terms of a bicyclopentane intermediate.<sup>6,7</sup> In one of these, the photolysis of a mixture of furan and diphenyloxadiazole in the presence of iodine gives

<sup>4</sup> A. Couture and A. Lablanche-Combiere, *J. C. S. Chem. Commun.*, 891 (1971); A. Couture, A. Delevallie, A. Lablanche-Combiere, and C. Parkanyi, *Tetrahedron* **31**, 785 (1975).

<sup>6</sup> E. E. van Tamelen and T. H. Whitesides, *J. Am. Chem. Soc.* **94**, 3894 (1968).

<sup>7</sup> O. Tsuga, K. Oe, and M. Tashiro, *Tetrahedron* **29**, 41 (1973).

some 3-benzoylfuran along with its benzoylhydrazone. Omission of the iodine affords the simple 1,2-addition compound as the sole product.<sup>7</sup>

1,2-Additions are common. Irradiation causes furan to add ketones to form bicyclic compounds with the two oxygen atoms always in adjacent positions. However, addition to photoexcited aldehydes, which are at a higher energy level and so discriminate less, gives both types of regioisomer.<sup>8,9</sup> The general oxetan structure (3) was first completely defined by Whipple and Evanega who used an interesting application of the pseudo-contact shift method; the ketone product possessed a pyridine residue so that an unambiguous interaction with Co(II) was present.<sup>9</sup> The direction of addition has been confirmed in various other ways, for example, by means of nuclear Overhauser enhancement.<sup>8</sup> Since acid-catalyzed ring fission converts the oxetans from aldehydes to 3-furylcarbinols (4) the method may have synthetic value when the effects of substituents are further explored.<sup>10</sup> Already it is clear that 2-methylfuran adds benzophenone on the same side as the alkyl group.<sup>8</sup>

The reactivity of furan is most often associated with triplet states. Calculations (INDO) of charge distribution agree with reactivities actually found, and triplet  $\sigma$ -complexes are suggested as key intermediates.<sup>11</sup> Low-lying triplet states have been detected in furan by variable-angle electron-impact spectroscopy (singlet  $\rightarrow$  triplet transitions are most intense at 3.99 and 5.22 eV).<sup>12</sup> Excited states may be quenched by furan without any indication of exciplex formation.<sup>13</sup>

In most aryl ketones the  $n \rightarrow \pi^*$  triplet is similar in energy to the lowest  $\pi \rightarrow \pi^*$  triplet and is responsible for the subsequent transformations; those ketones with  $\pi \rightarrow \pi^*$  as the lowest triplet state are relatively unreactive photochemically. Alkyl furyl ketones belong to this last group; their photochemical activity is centered on the furan double bonds rather than on the carbonyl group. This is consistent with the long-lived phosphorescence exhibited by such compounds. 2-Acetylfuran, for example gives with methylpropene a mixture in which the main isomer has structure 5.<sup>14</sup> By contrast, the addition of dimethylbutene to 2-benzoylfuran discloses a return to the

<sup>8</sup> C. Rivas and E. Payo, *J. Org. Chem.* **32**, 2918 (1967); T. Nakano, C. Rivas, C. Perez, and K. Tori, *J. C. S. Perkin I*, 2323 (1973).

<sup>9</sup> E. B. Whipple and G. R. Evanega, *Tetrahedron* **24**, 1299 (1968).

<sup>10</sup> A. Zamojski and T. Kozluk, *J. Org. Chem.* **42**, 1089 (1977).

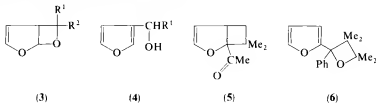
<sup>11</sup> I. A. Abronin, L. I. Belen'kii, and G. M. Zhidomirov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 588 (1977).

<sup>12</sup> W. M. Flicker, A. O. Mosher, and A. Kupperman, *Chem. Phys. Lett.* **38**, 489 (1976).

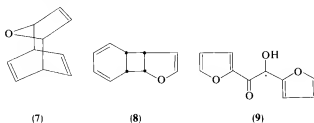
<sup>13</sup> M. E. Sime, D. Phillips, and K. Al-Ani, *Mol. Photochem.* **7**, 149 (1976).

<sup>14</sup> T. S. Cantrell, *J. C. S. Perkin I*, 155 (1972).

more common situation and the primary product is oxetane **6**<sup>14</sup> resulting from addition to the carbonyl group.



The photochemical 1,4-addition of dimethyl acetylenedicarboxylate to furan has been compared with the purely thermal addition.<sup>15</sup> Even the 1,4-addition (in both components) of furan to benzene is possible.<sup>16</sup> It is promoted by irradiation at 254 nm. Adduct **7** dissociates into its components when heated or irradiated in the presence of acetone, but simple irradiation or heating to 60°C also induces a Cope rearrangement leading to isomer **8** corresponding to a 1,2-addition product. Thus, the survival of the original adduct is largely due to the screening effect of benzene. The use of GLC as a method of analysis fails to disclose the main products at all, owing to thermal degradation. Photochemical products are obtained as their adducts with silver nitrate or maleic anhydride.

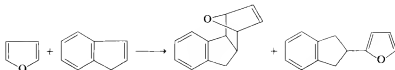


The idea that electron-rich compounds such as furan might undergo cycloaddition with other electron-rich species has been slow to gain recognition. A suitable electron acceptor has to be present, aromatic nitriles being favored. In the presence of 1-naphthalenecarbonitrile, furan and indene react to give two main products (Scheme 3).<sup>17</sup> Styrenes can replace indene, and 2-methylfuran the unsubstituted heterocycle. But 2,5-dimethylfuran not only does not undergo such photoaddition, but it also quenches the reaction. In acetonitrile, the fluorescence of the aromatic nitriles is quenched by furan

<sup>15</sup> R. P. Gandhi and V. K. Chadha, *J. C. S. Chem. Commun.*, 552 (1968).

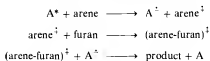
<sup>16</sup> J. Berridge, D. Bryce-Smith, and A. Gilbert, *J. C. S. Chem. Commun.*, 964 (1974), with T. S. Cantrell, *ibid.*, 611 (1975).

<sup>17</sup> K. Mizuno, R. Kaji, H. Okada, and Y. Otsuji, *J. C. S. Chem. Commun.*, 594 (1978).



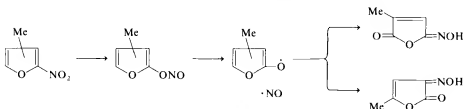
SCHEME 3

and its derivatives, a fact which, with other information, leads to the conclusion that such photoreactions have electron-transfer mechanisms. Thus, the cation radical from 2,5-dimethylfuran is very easily formed, but it is too stable to participate further. Japanese workers suggest the following mechanism where A is the aromatic nitrile electron acceptor:



According to this, the furan reacts with a radical-cation. Another Japanese group has suggested a more complex sequence to explain why benzene-1,4-dicarbonitrile comes to be attacked by furan in methanol with loss of one cyanide group. This reaction is promoted by phenanthrene; and on chromatography, the product loses the methanol to give 4(2-furyl)benzonitrile.<sup>18</sup>

The photochemistry of substituted furans can be very complex indeed and may differ considerably from that found for benzenoid compounds. However, the photocyclization of 2,2'-ethylenedifuran to a benzodifuran is a simple reaction that is an exact counterpart to the photocyclization of stilbene to phenanthrenes.<sup>19</sup> Some side chains allow ready dissociation to radicals; typical is the nitro group and Scheme 4 displays what happens to irradiated



SCHEME 4

2-nitrofuran.<sup>20</sup> A comparison should be made with Scheme 50 in Part I (Vol. 30) which is concerned with the action of radicals on nitrofurans.

<sup>18</sup> C. Pac, A. Nakasone, and H. Saburai, *J. Am. Chem. Soc.*, **99**, 5806 (1977).

<sup>19</sup> R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).

<sup>20</sup> R. Hunt and S. T. Reid, *J. C. S. Perkin I*, 2527 (1972).

The location of the oxime group in the product in Scheme 4 depends upon where the methyl group is located, but the yields can be high (79%). Irradiation of 2-methoxyfuran also induces side-chain dissociation and the formation of lactones (i.e., methylbutenolides).<sup>21</sup> Here the abundant formation of ethane testifies to the participation by methyl radicals. Such reactions are too complex for synthetic purposes. This is true also of 2-acetoxymethylfuran photochemistry in which the photo-Fries reaction is not observed.<sup>21</sup> Curiously, furan itself sensitizes the photo-Fries reaction in benzenoid esters.<sup>22</sup>

Furan-2-carbaldehyde has been much studied. A thorough analysis of the first two major electronic transitions has been carried out. Practical work is hampered by the resinification of the compound and by the presence of a trace impurity which gives rise to a long-lived pressure-independent component in the phosphorescence spectrum.<sup>23</sup> The absence of  $n \rightarrow \pi^*$  excited emission and other facts implicate a very efficient double intersystem crossing.<sup>14,24</sup> Whether or not sensitized by mercury, photodecomposition of the aldehyde gives much carbon monoxide, propyne, and allene. Small amounts of furan, carbon dioxide, and acetylene are also formed.

The photoreduction of furil in 2-propanol as solvent and proton donor within the cavity of an ESR spectrophotometer allows the existence of a radical to be demonstrated.<sup>25</sup> This radical is formally identical with the chemically generated radical in Scheme 60 (Part I). With the stronger acid, phenol in place of the alcohol three radicals appear; compound **9** is one.<sup>25</sup> With pentachlorophenol the product is found to be spin polarized; CIDNP spectra show that initially emissive protons relax to enhanced absorption and *vice versa*.<sup>26</sup>

The photooxidation of 2,5-di-*t*-butylfuran by singlet oxygen is believed to give an endoperoxide similar to **136** (see Part I) in the course of the formation of acyclic di- and triketones. The reaction is used to examine the efficiency of aromatic sensitizers.<sup>27</sup> The photooxidation of 3-alkylfurans was mentioned in Section I,B,1. Arrhenius parameters for the similar addition of singlet oxygen to furan and to 2-methylfuran in the gas phase have been obtained. To explain the large rate increase along with a decrease in activation energy when the reaction is conducted in solution it is suggested that a

<sup>21</sup> S. Srinivasan and H. Hiraoka, *Tetrahedron Lett.*, 2767 (1969).

<sup>22</sup> A. Melhorn, B. Schwenzer, H.-J. Bruckner, and K. Schwetlick, *Tetrahedron* **34**, 481 (1978); A. Melhorn, B. Schwenzer, and K. Schwetlick, *ibid.* **33**, 1483 (1977).

<sup>23</sup> R. Zwarich and I. Rabinowitz, *J. Chem. Phys.* **63**, 4565 (1975).

<sup>24</sup> A. Gandini, J. M. Parsons, and R. A. Back, *Can. J. Chem.* **54**, 3089, 3095 (1976).

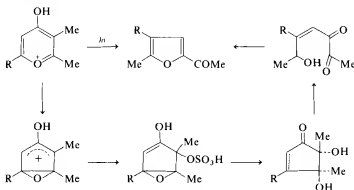
<sup>25</sup> A. J. Elliot and J. K. S. Wan, *Can. J. Chem.* **56**, 2499 (1978).

<sup>26</sup> J. W. M. Debner, D. A. Hutchinson, and J. K. S. Wan, *Chem. Phys. Lett.* **62**, 300 (1979); with R. Hardy, *Chem. Phys.* **43**, 81 (1979).

<sup>27</sup> A. A. Gorman, I. R. Gould, and I. Hamblett, *Tetrahedron Lett.*, 1087 (1980).

charge-transfer mechanism is operating. Discussion is hampered by the fact that in this reaction the LUMO on oxygen lies below the HOMO for the diene component and not, as is more usual, above it.<sup>28</sup>

Since many furans are not particularly sensitive to light they often form as products of photochemical reactions. A high pressure mercury arc can be used to eject nitrogen from pyridazine *N*-oxides and form cyclopropenyl ketones and their furan isomers.<sup>29</sup> High yields of 2-acetylfuran can be achieved by irradiating the pyrilium ion in Scheme 5 (i.e., the requisite pyrone dissolved in sulfuric acid) although the conditions, mainly the acidity, have to be carefully controlled.<sup>30</sup> Surprisingly, the intermediate cyclopentenone diol can be isolated; with 50% sulfuric acid it is converted to the furan in a separate step.



SCHEME 5

## II. Cycloadditions

### A. INTERMOLECULAR ALKENE ADDITIONS

The well-known 1,4-cycloadditions to furan have been accorded much attention for both theoretical and synthetic reasons. The archetype, the addition of maleic anhydride, was studied long ago by Woodward and Bauer

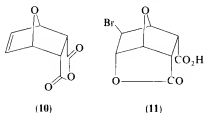
<sup>28</sup> R. D. Ashford and E. A. Ogryzlo, *Can. J. Chem.*, **52**, 3544 (1974).

<sup>29</sup> T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron*, **56**, 2747 (1973).

<sup>30</sup> J. W. Pavlik, R. R. Bolin, K. C. Bradford, and W. C. Anderson, *J. Am. Chem. Soc.*, **99**, 2816 (1977); J. W. Pavlik and A. P. Spada, *Tetrahedron Lett.*, 4441 (1979) J. A. Barltrop, A. C. Day, and C. J. Samuel, *J. C. S. Chem. Commun.*, 823 (1976).

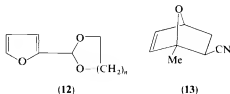
who proved that the only known product was the *exo*, not the *endo*, isomer as previously thought. It was later suggested that the *exo* isomer is formed faster than the *endo*, the *exo* being gradually converted to the *endo* isomer. Lee and Herndon have now pointed out that the faster formation of the *exo* isomer would actually disobey the Alder rules since the secondary interactions are minimal; they have demonstrated by means of NMR spectroscopy that the *endo* isomer (**10**) is after all the primary product, although it does convert to the *exo* isomer as time goes on.<sup>31</sup>

The furan slowly dissolves in water on addition of bromine to give lactone **11** derived from the *endo*-dicarboxylic acid. The acid itself has been isolated



with difficulty. The *exo* isomer was not noted. The same study disclosed that dimethyl maleate requires several months to add to furan. The addition of dimethyl fumarate is faster but reaches an equilibrium.<sup>32</sup>

A dispute about the configuration of the substance formed from maleic anhydride and ketals (**12**) in ether at 0°C has been terminated by evidence that the products are mixtures.<sup>33</sup> A more general study indicates that, with maleic anhydride, substituted furans almost always supply in the first stage a 1:1 adduct apparently formed by way of a charge-transfer complex.<sup>33</sup> Detailed structural studies have established that the substituents may exert steric effects able to influence individual rates of formation; the resulting *endo*-*exo* ratios have been determined.<sup>34</sup> Rate studies with *para*-substituted



<sup>31</sup> M. W. Lee and W. C. Herndon, *J. Org. Chem.* **43**, 518 (1978).

<sup>32</sup> T. A. Eggelte, H. de Koning, and H. C. Huisman, *Tetrahedron* **29**, 2491 (1973).

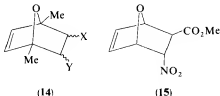
<sup>33</sup> J. Maslinska-Solich and Z. Jedlinska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **22**, 749 (1974).

<sup>34</sup> J. Maslinska-Solich, *J. C. S. Perkin I*, 606 (1975); *Rocz. Chem.* **49**, 611 (1975).

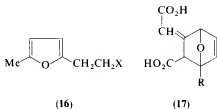


2-phenylfurans show that, as expected for a concerted mechanism, substituents exert only slight effects upon the addition of dimethyl acetylenedicarboxylate.<sup>35</sup>

2-Methylfuran adds propenenitrile giving all four (regio + stereo) isomers. The major one has structure **13** which with *t*-butoxide ion provides 2-methylbenzonitrile in high yield.<sup>36</sup> Such routes to benzenoid compounds have considerable potential. At normal pressure the 7-oxabicyclo[2.2.1]heptane adducts (**14**) from 2,5-dimethylfuran can be procured only by the use of enes with two activating groups, X and Y. But at 15000 atm, even monoactivated enes react smoothly at room temperature.<sup>37</sup> Nitroalkenes have been little studied. Methyl 3-nitropropenoate readily adds furan giving **15** as the first stage in a synthesis of *dl*-2'-deoxyshowdomycin; the product equilibrates readily with its epimer.<sup>38</sup>



When strongly electron-withdrawing substituents activate the alkene, the division between cycloadditions and what appear to be electrophilic substitutions becomes very narrow. We have already touched upon the ambiguous behavior of diazonium salts in Section V.A, Part I (cf. structure **104**, in Part I). Whereas furan adds propenoyl chloride or nitroethene in the endo-1,4 mode, 2-methylfuran undergoes substitution to give 2,5-disubstituted furans (**16**).<sup>38a</sup> Tetracyanoethylene also reacts by substitution instead of addition.



<sup>35</sup> D. C. Ayres and J. R. Smith, *J. C. S. Chem. Commun.*, 886 (1967).

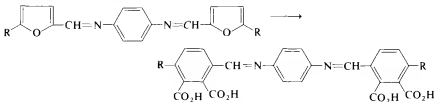
<sup>36</sup> K. Kienzie, *Helv. Chim. Acta* **58**, 1180 (1975).

<sup>37</sup> W. G. Dauben and H. C. Krabbenhoft, *J. Am. Chem. Soc.* **98**, 1992 (1976); J. Rimmelin, G. Jenner, and P. Rimmelin, *Bull. Soc. Chim. Fr.* **2**, 461 (1978).

<sup>38</sup> G. Just and M.-I. Lim, *Can. J. Chem.* **55**, 2993 (1977).

<sup>38a</sup> T. A. Eggelte, H. de Koning, and H. C. Huisman, *Heterocycles* **4**, 19 (1976).

A double furanoid Schiff base has been transformed into its benzene analog (Scheme 6) by means of maleic anhydride<sup>39</sup>; more generally and more directly alkynes are employed for this purpose (see below).

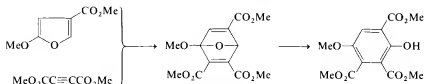


SCHEME 6

Allenes are rarely used. The trimethylsilyl ester of prop-2,3-diendioic acid adds but once to 5-substituted furans giving adducts (17) intended for use in the synthesis of *Rauwolfia* alkaloids.<sup>40</sup>

## B. INTERMOLECULAR ALKYNE ADDITIONS

The typical transformation of a furan to a benzene derivative shown in Scheme 7 was reported by Abbott *et al.*<sup>41</sup> Here ether fission was spontaneous



SCHEME 7

because the methoxy group assists it; acid treatment is usually required. Occasionally, very resistant ethers are encountered; for example, Sargent and co-workers found the dual ether obtained from 2,2'-difuran and methyl butynedioate to be quite remarkably stable to acids.<sup>42</sup>

Acetylenic monoesters are much less reactive and add only slowly to simple furans, so McCulloch and Innes have exploited the outstanding catalytic effect of aluminium chloride upon Diels-Alder additions. Not only

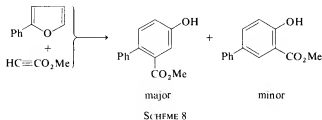
<sup>39</sup> A. A. Barlin, B. I. Liogon'skii, B. I. Zapadinskii, E. A. Kozantseva, and A. O. Stankevich, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 867 (1977).

<sup>40</sup> T. Suzuki, S. Kagaya, A. Tomino, K. Unno, T. Kametani, T. Takahashi, and Y. Tamaka, *Heterocycles* **9**, 1749 (1978).

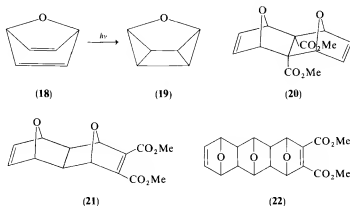
<sup>41</sup> P. J. Abbott, R. M. Acheson, R. F. Flowerday, and G. W. Brown, *J. C. S. Perkin I*, 1177 (1974).

<sup>42</sup> R. Grigg, P. Roffey, and M. V. Sargent, *J. Chem. Soc. C*, 2327 (1967).

does the catalyst increase the rate of reaction dramatically,<sup>43</sup> it also emphasizes any regiospecificity, as can be seen from the example sketched in Scheme 8.<sup>44</sup>



From the slow, noncatalyzed reactions, derivatives of 7-oxabicyclo[2.2.1]hepta-2,5-diene (**18**) may be obtained. UV irradiation does not reverse the addition but allows an easy entry into the 3-oxaquadricyclane series (**19**).<sup>45</sup> When furan adds to an acetylenic diester the product is still reactive enough to add another molecule of furan, a somewhat unexpected feature being that the product (**20**) is obtained only at lower temperatures. Above 100° C dissociation must occur and the less active double bond takes up the alkyne to give the thermodynamically more stable isomer (**21**).<sup>43</sup> Whatever the addition, mixtures of endo and exo configurations result. The result is thought to reflect the fact that geometrical overlap of orbitals at the primary reaction centers is more important than secondary interactions as bond formation



<sup>43</sup> A. W. McCulloch, D. G. Smith, and A. G. McInnes, *Can. J. Chem.* **51**, 4125 (1973); **52**, 1013 (1974).

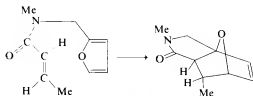
<sup>44</sup> A. W. McCulloch and A. G. McInnes, *Can. J. Chem.* **49**, 3152 (1971); **53**, 1496 (1975).

<sup>45</sup> H. Hogeveen and B. J. Nusse, *J. Am. Chem. Soc.* **100**, 3110 (1978).

occurs.<sup>43,46</sup> Furan itself will continue to add; **22** has been isolated, but substituted furans are much less reactive and 2,5-dialkylfurans add only slowly, no reaction beyond the first addition having been observed.<sup>47</sup>

### C. INTRAMOLECULAR ADDITIONS

Intramolecular cycloaddition has special features depending upon the way in which the chain that links a diene center to a dienophile center increases the probability of a useful collision. At the same time a variety of constraints that are present in the transition state affect regiospecificity and exo/endo ratios. Few detailed studies are available. However, ester and secondary amide groups in the linking chain have been found to slow or stop the addition because, it is thought, they impose an unfavourable conformation upon the system. Purely carbon chains or those containing *t*-amide functions undergo cycloaddition satisfactorily.<sup>48</sup> Only the exo product is seen (Scheme 9). The new ring formed in the cycloaddition can be 5-, 6-, or



SCHEME 9

7-membered, and whereas  $\alpha$ -substituents attached to the ene have little effect  $\beta$ -substituents severely reduce the rate.<sup>48</sup> Yet a similar internal addition occurs at 90°C in a quaternary ammonium-linked system notwithstanding the double terminal substitution of its alkene component.<sup>49</sup>

A competition between two kinds of cycloaddition is observable in some compounds. In a rather unusual case intramolecular addition predominates if the compound is left at room temperature in  $\text{CH}_2\text{Cl}_2$  containing florasil, whereas the intermolecular addition is promoted by heating the compound in boiling xylene.<sup>50</sup>

<sup>46</sup> W. C. Herndon, *Chem. Rev.* **72**, 157 (1972).

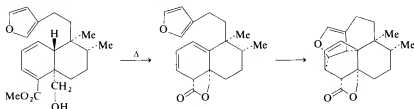
<sup>47</sup> J. O. Slee and E. LeGoff, *J. Org. Chem.* **35**, 3897 (1970).

<sup>48</sup> K. A. Parker and M. R. Adamchuk, *Tetrahedron Lett.*, 1689 (1978); H. W. Gschwend, M. J. Hillman, B. Kisis, and R. K. Rodebaugh, *J. Org. Chem.* **41**, 104 (1976).

<sup>49</sup> G. O. Torosyan, S. L. Paravyan, R. S. Mkrtchyan, K. Ts. Tagmazyan, and A. T. Babayan, *Arm. Khim. Zh.* **32**, 182 (1979).

<sup>50</sup> P. J. de Clerq and L. A. van Royen, *Synth. Commun.* **9**, 771 (1979).

A striking example of the special effects produced by intramolecular cycloaddition is discussed by Ghisalberti *et al.*<sup>51</sup> who pointed out that, if correctly poised, the furan ring can act as the dienophile instead of the diene component (Scheme 10). Otherwise the ability of furan to act as the dienophile



SCHEME 10

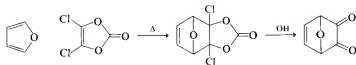
component is known only in certain reactions with 1,2-quinones, which lead to dioxan derivatives [as mentioned in Section VI,B,1 (Vol. 30)] with nitrile oxides (as described below) and in the special case of certain derivatives of amino furan.

Japanese workers found that magnesium ion strongly accelerates internal cycloaddition in *ortho*-phenolic amides perhaps by acting as a coordinating center.<sup>52</sup> General discussions of internal cycloaddition are available.<sup>53</sup>

## D. TRANSIENT SPECIES AND SPECIAL CASES

### 1. Dienophile Activation

The dienophile used for reaction with furans is almost always activated by carbonyl, cyano, nitro, and similar  $\pi$ -electron withdrawing substituents, despite the fact that theory clearly points to the possibility of other means of activation. In the apparently unique example shown in Scheme 11 the



SCHEME 11

<sup>51</sup> E. L. Ghisalberti, P. R. Jeffries, and T. G. Payne, *Tetrahedron* **30**, 3099 (1974); A. S. Onishchenko, "Diene Synthesis," Chapter VII, p. 556. Israel Program for Scientific Translations, Jerusalem, 1964.

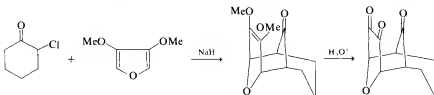
<sup>52</sup> T. Mukaijama, T. Tsuji, and N. Iwasara, *Chem. Lett.*, 697 (1979).

<sup>53</sup> W. Oppolzer, *Angew. Chem., Int. Ed. Engl.* **16**, 10 (1977).



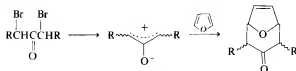
### 3. Other Transient Species

2,3-Pyridyne has proved elusive, but the brief existence of a derivative has been demonstrated through its reaction with furans.<sup>63</sup> Favorskii intermediates and similar three-carbon transients<sup>64</sup> have been found to add readily to furans in several studies; an example used for synthetic purposes by Matzinger and Eugster produced the tricyclic triketone shown in Scheme 12.<sup>65</sup> Very similar reactions occur with the transients formed by treating



SCHEME 12

$\alpha,\alpha'$ -dibromoketones with diiron nonacarbonyl (Scheme 13).<sup>66</sup> Although



SCHEME 13

addition is believed to be concerted there is no strict stereochemical control because epimeric mixtures are produced; but both primary and secondary FMO interactions are important and orientational preferences are consistent with a need to maximize stabilization in zwitterionic intermediates.<sup>66</sup> The simplest dibromoketone, 1,3-dibromopropanone, gives poor results with furans bearing alkyl groups, and a diversion via the tetrabromoketone was required for a satisfactory synthesis of the natural tropone, nezukone (**26**), from 2-isopropylfuran by this route.<sup>66</sup> The 2-methoxyallyl cation adds to furan similarly.<sup>67</sup> Some apparent electrophilic substituent reactions of furan might actually involve cycloaddition followed by ring opening. This is particularly true for allylic carbonium ions, as shown in Scheme 14.<sup>67a</sup>

<sup>63</sup> J. D. Cook and B. J. Wakefield, *J. C. S. Chem. Commun.*, 297 (1968).

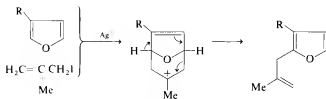
<sup>64</sup> B. Fohlsch, D. Lutz, W. Gottstein, and U. Dukek, *Justus Liebigs Ann. Chem.*, 1847 (1977).

<sup>65</sup> P. Matzinger and C. H. Eugster, *Helv. Chim. Acta* **62**, 2325 (1979).

<sup>66</sup> R. Noyori, S. Makino, T. Okita, and Y. Hayakawa, *J. Org. Chem.* **40**, 806 (1975); R. Noyori, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1741 (1973); Y. Hayakawa, M. Sakai, and R. Noyori, *Chem. Lett.*, 509 (1975).

<sup>67</sup> A. E. Hill, G. Greenwood, and H. M. R. Hoffmann, *J. Am. Chem. Soc.* **95**, 1338 (1973).

<sup>67a</sup> H. M. R. Hoffmann and N. P. Janes, *J. Chem. Soc. C*, 1456 (1969); *J. Chem. Soc. B*, 57 (1968).

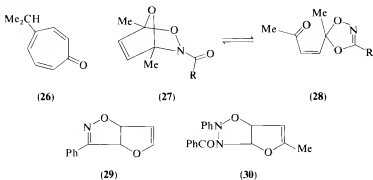


SCHEME 14

#### 4. Addenda Containing Heteroatoms

Nitrosocarbonyl compounds, prepared by the oxidation of hydroxamic acids with silver oxide, add to 2,5-dimethylfuran to give adducts (**27**) in the expected way, but these immediately rearrange to 1,4,2-dioxazoles (**28**). A special feature is that the reaction must be easily reversible since heating the adducts causes them to eliminate dimethylfuran, leaving the nitrosocarbonyl intermediate to be trapped by some other means.<sup>68</sup>

Nitrile oxides add in the 1,2- but not the 1,4-mode, to furans. Frontier orbital analysis has been called upon to explain why the addition shows a regioselectivity favoring a large preponderance of isomer **29**. As with many electron-demanding reagents, the oxides add only to the substituted double bond in 2-methylfuran.<sup>69</sup> A similar addition occurs when 2-methylfuran accepts in the absence of light an acylnitrone such as  $\text{PhCON}=\text{N}(\text{O})\text{Ph}$  to give (mainly) product **30**.<sup>70</sup>



Zefirov has discussed both 1,4- and 1,2-additions of aliphatic azo compounds to furans.<sup>71</sup>

<sup>68</sup> C. J. B. Dobbin, D. Mackay, M. R. Penney, and L. H. Dao, *J. C. S. Perkin I*, 703 (1977).

<sup>69</sup> P. Caramella, G. Cellerino, A. C. Coda, A. G. Invernizzi, P. Grunager, K. N. Houk, and F. M. Abini, *J. Org. Chem.* **41**, 3349 (1976).

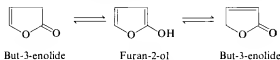
<sup>70</sup> L. Fiserá, J. Kovács, and J. Polhačiková, *Heterocycles* **12**, 1005 (1979).

<sup>71</sup> N. S. Zefirov, *Zh. Org. Khim.* **3**, 427 (1967); N. S. Zefirov and A. A. Dudinov, *ibid.*, 428.



### III. Furanols, Furanamines, and Furanthiols

Since in the free state simple furanols (hydroxyfurans) tautomerize to the carbonyl form more or less completely we need to consider butenolides and related compounds (Scheme 15). We propose, however, to observe the



SCHEME 15

nearly universal practice of regarding butenolides simply as lactones and not (as in Beilstein and *Chemical Abstracts*) as derivatives of furan. (Compounds named as butenolides are numbered from the carbonyl carbon as position 1; named as furans they are numbered from the ring oxygen atom as 1). The dividing line is hazy because of the prevalence of lithiation techniques that convert lactones directly to enolates with, presumably, most of the charge on oxygen and therefore with a furan nucleus. Enol ethers and other derivatives that cannot attain the carbonyl form have a furan structure. Similarly, the chemistry of furanamines and furanthiols is considered to be that of a furan. Butenolides have an extensive literature of their own that has been reviewed.<sup>72-74</sup>

#### A. FURAN-2-OL AND FURAN-2,5-DIOL

##### 1. *Furan-2-ol*

The question of enolization in butenolides remains a matter of some theoretical interest; and recently, with the advent of lithiation and allied techniques, it has become more pointed. Scandinavian workers have determined the ionization potentials of certain butenolides and found them to lie at or above 9.6 eV; a furan-2-ol would be expected to have much lower IP of about 8.4 eV and since no peak was noted in this region it follows that the butenolides are not appreciably enolized in the gas phase.<sup>75</sup> At high temperatures (near 500°C) butenolides suffer cheletropic elimination of carbon monoxide giving vinylic ketones in good yield—again enols play no part.<sup>76</sup>

<sup>72</sup> Y. S. Rao, *Chem. Rev.* **76**, 632 (1976).

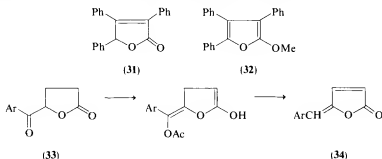
<sup>73</sup> A. A. Avetisyan and M. T. Dangyan, *Russ. Chem. Rev. (Engl. Transl.)* **46**, 643 (1977).

<sup>74</sup> G. Pattenden, *Prog. Chem. Org. Nat. Prod.* **35**, 133 (1978).

<sup>75</sup> O. Thörstad, K. Undheim, B. Cederland, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B28**, 647 (1975).

<sup>76</sup> W. Skorianetz and G. Ohloff, *Helv. Chim. Acta* **58**, 1272 (1975).

And Padwa and his colleagues have been able to explain the characteristic photochemistry of butenolides without observing any feature that might have indicated that enolization or aromatization is of importance.<sup>77</sup> Enolization does occur in butenolides if the new double bond permits more extensive conjugation or delocalization in addition to that associated with furan aromaticity, as in the case of 1-benzofuran-2(3*H*)-ones.<sup>78</sup> Enolization is also encountered in butenolides bearing several phenyl substituents. For example, with potassium in benzene the butenolide (31) yields a yellow salt that is converted to the methoxyfuran (32) by methyl sulfate, as well as suffering C-methylation by iodomethane.<sup>79</sup> Moreover, butenolides react with Grignard reagents at the carbonyl groups to give adducts, but with lithium aluminium hydride they yield products having a reduced alkene bond, presumably because in the enolic form the carbonyl is effectively protected.<sup>80</sup> Again, enolization seems to explain what happens when the lactone (33) is heated with an acetylating mixture consisting of acetic anhydride with either sodium acetate or an acid catalyst; enolization, O-acetylation, prototropy, and finally an elimination may occur to produce the 5-arylidenefuran-2-one (34).<sup>81</sup> The product is a butenolide like those that



occur to a limited extent in nature, and the reaction has been used to synthesise one of them.<sup>81</sup> Scheme 16 shows the key step in the synthesis of such a compound, freelingyne (86 in Part I), by a method that relies upon a butenolide phosphorane to create the exocyclic alkene link.<sup>82</sup> Of course, the phosphorus ylide can be regarded as an enolate anion with the charge mainly on oxygen and therefore as a true furan.

<sup>77</sup> A. Padwa, T. Brookhart, D. Dehm, G. West, and G. Wubbels, *J. Am. Chem. Soc.* **99**, 2347 (1977); A. Padwa, T. Brookhart, D. Dehm, and G. Wubbels, *ibid.* **100**, 8247 (1978).

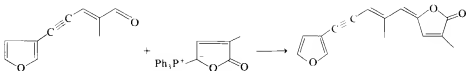
<sup>78</sup> J. A. Elix and B. A. Ferguson, *Aust. J. Chem.* **26**, 1079 (1973).

<sup>79</sup> G. Rio and J.-C. Hardy, *Bull. Soc. Chim. Fr.*, 3572 (1970).

<sup>80</sup> D. K. Dikshit, K. L. Munshi, R. S. Kapil, and N. Anand, *J. C. S. Perkin I*, 1087 (1977).

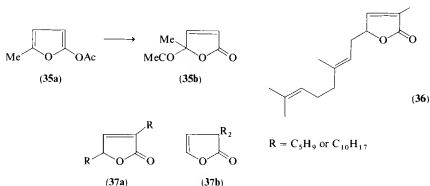
<sup>81</sup> K. Yamada, Y. Togawa, T. Kato, and Y. Hirata, *Tetrahedron* **27**, 5445 (1971).

<sup>82</sup> D. W. Knight and G. Pattenden, *J. C. S. Chem. Commun.* 188 (1974).



SCHEME 16

Strong, nonnucleophilic bases readily convert butenolides to enolate anions. Reaction of 4-methylbut-3-enolide with lithium diisopropylamide followed by acetic anhydride gives 5-methyl-2-furyl acetate (**35a**) which undergoes useful cycloaddition and rearrangement reactions, especially a rearrangement to the 5-acetylfuran-2(5*H*)-one (**35b**) that is catalyzed by boron fluoride.<sup>83</sup> Similarly, 3- and 4-methylfuran-2(5*H*)-one afford enolates that react with prenyl bromide and similar reagents providing neat routes to several natural products including freelingite (**36**) and rosefuran (**48** in Part I). Whether the incoming alkyl group occupies the 3- or the 5- position is mainly determined by the substituents already present; methyl substituents favor 3-alkylation and a 4-methoxy group favors 5-alkylation of the furan-2-one ring. If there are no substituents it becomes surprisingly difficult to avoid bisalkylations giving **37a** and **37b**; this is both an interesting finding and an unfortunate limitation.<sup>83a</sup>



Ethers can be obtained most easily by alkylating the enols as noted above, from cycloadditions to alkoxyisoxazoles (Section II,H, Part I), and from 2,2-<sup>84</sup> or 2,5-dimethoxydihydrofurans, the latter being easily accessible by the methoxylation of furans (Sections VI,A,1 and VI,B,1, Part I) a method that has been neatly adapted to a synthesis of 3-bromo-2-methoxyfuran.<sup>85</sup>

<sup>83</sup> G. A. Kraus and B. Roth, *J. Org. Chem.* **43**, 2072 (1978).

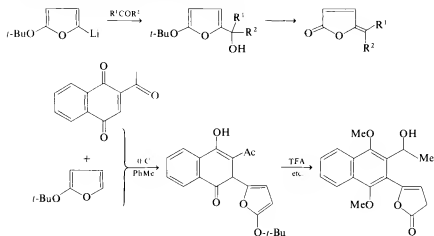
<sup>83a</sup> D. R. Gedge and G. Pattenden, *Tetrahedron Lett.*, 4443 (1977).

<sup>84</sup> R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.* **97**, 1317 (1967).

<sup>85</sup> E. McDonald, A. Suksamran, and R. D. Wylie, *J. C. S. Perkin I*, 1893 (1979).

A few 2-alkoxyfurans are accessible from the cycloaddition of ynes to ester carbonyl functions.<sup>86</sup> Replacement reactions at the furan nucleus do give alkoxyfurans but are variable in their ability to yield aryloxyfurans.<sup>86a</sup>

2-*t*-Butoxyfuran is readily available and has been recommended for various condensation reactions as a butenolide synthon. Lithiation by *t*-butyllithium occurs at the 5-position, and condensation with aldehydes or ketones followed by acid hydrolysis leads to useful 5-alkylidenefuran-2(5*H*)-ones.<sup>87</sup> The alkoxyfuran will also add smoothly to electron-deficient quinones where the lithium enolates prove to be too basic and destroy them.<sup>87</sup> Examples of these reactions are depicted in Scheme 17.



SCHEME 17

2-Methoxyfurans are not particularly efficient as diene components in cycloadditions to electron-deficient dienophiles, although furan-2,5-dione adds readily to 3-bromo-2-methoxyfuran.<sup>85</sup> On the contrary, in 2-methoxyfuran the 2,3-double bond itself possesses an electron-density high enough to enable it to act as a dienophile with an electron-deficient component (e.g., a tetrazine diester).<sup>88</sup>

Acid hydrolysis of 2-alkoxyfurans easily generates a butenolide, a pathway which allows the introduction of various substituents into a butenolide ring. Protonation at the 5 position is the rule and leads via a 2-butenolide to an acrylate; 3-protonation is minor and never results in a butenolide

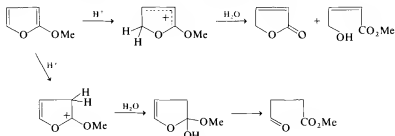
<sup>86</sup> R. Gericke and F. Winterfeldt, *Tetrahedron* **27**, 4109 (1971).

<sup>86a</sup> R. Kada and J. Kovac, *Chem. Zvesti* **29**, 402 (1975); K. E. Kolb and C. L. Wilson, *J. Chem. Soc. Chem. Commun.*, 271 (1966).

<sup>87</sup> G. A. Kraus and H. Sugimoto, *J. C. S. Chem. Commun.*, 30 (1978).

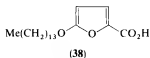
<sup>88</sup> G. Seitz and T. Kaempchen, *Arch. Pharm. (Weinheim, Ger.)* **311**, 728 (1978).

but only in ring opening to saturated aldehyde esters. Both modes are outlined in Scheme 18.<sup>89</sup> The sensitivity of such ethers to acid does not

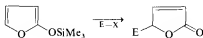


SCHEME 18

preclude the existence of compounds such as **38**, which inhibits hepatic lipogenesis in rats.<sup>90</sup>



The newest techniques employ silylation. Even the anions of saturated butenolides afford the enol ester on reaction with chlorotrimethylsilane<sup>91</sup>; applied to a butenolide the method readily supplies a 2-silyloxyfuran. Such ethers are even more easily procured by allowing a butenolide to react with chlorotrimethylsilane in the presence of triethylamine and zinc chloride; but for reasons that remain unclear, acetonitrile is the only satisfactory solvent.<sup>92</sup> A typical transformation of 2-trimethylsilyloxyfuran is shown in Scheme 19.



SCHEME 19

## 2. Furan-2,5-diol

This structure is most commonly found as the monocarbonyl form (**39**), a hemiacetal which behaves as such. Hydrolysis opens the ring, whereas

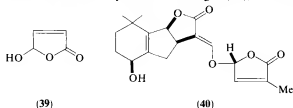
<sup>89</sup> J. E. Garst and G. L. Schmir, *J. Org. Chem.*, **39**, 2920 (1974).

<sup>90</sup> S. A. McCune and R. A. Harris, *J. Biol. Chem.*, **254**, 10095 (1979).

<sup>91</sup> J. K. Rasmussen and A. Hassner, *J. Org. Chem.*, **39**, 2558 (1974).

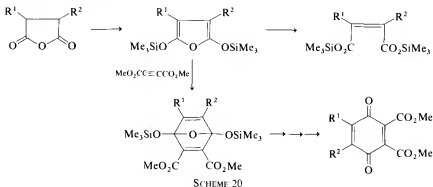
<sup>92</sup> M. Asaoka, N. Sugimura, and H. Takei, *Bull. Chem. Soc. Jpn.*, **52**, 1953 (1979); M. Asaoka, F. Miyake, and H. Takei, *Chem. Lett.*, 167, (1977); E. Yoshii, T. Koizumi, E. Kitatsuji, T. Kawazoe, and T. Kaneko, *Heterocycles*, **4**, 1663 (1976).

ethanol and acid furnish the ethyl ether and hydrogen bromide the 4-bromobutenolide.<sup>93</sup> A similar halogen compound, 4-bromo-2-methylbutenolide, prepared most simply by bromination of 3-methylfuran-2(5H)-one, was instrumental in two syntheses of strigol (40), the extraordinarily



potent germination trigger exuded by the rootlets of plants susceptible to attack by the semiparasite *Striga lutea* Lour. (witchweed).<sup>94</sup> Alternatively, hemiacetals (39) can be obtained by the cyclization of unsaturated ketonic acids or by the oxidation of furans.<sup>94a</sup>

A promising innovation by Brownbridge and Chan applies the silylation reaction to succinic anhydride (3,4-dihydrofuran-2,5-dione); both carbonyl groups enolize giving 2,5-bistrimethylsilyloxyfuran in very high yield.<sup>95</sup> Such esters are very sensitive to water and also to oxygen, which rapidly converts them into trimethylsilyl maleates by an unknown route. The bis-silyl ethers are better than furan for cycloadditions because they react readily even with monoactivated alkenes, thus allowing ready access to a variety of quinones (Scheme 20).



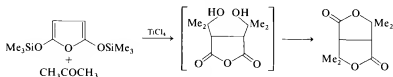
<sup>93</sup> I. L. Dover and R. E. Willette, *J. Org. Chem.* **38**, 3878 (1973); F. Farina, M. R. Martin, and H. V. Martin, *An. Quim.* **74**, 144, 799 (1978).

<sup>94</sup> G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, and H.-J. Wild, *J. C. S. Chem. Commun.*, 834 (1974); J. B. Heather, R. S. D. Mittal, and C. J. Shih, *J. Am. Chem. Soc.* **98**, 3661 (1976).

<sup>94a</sup> S. Torii, H. Tanaka, and T. Okamoto, *Bull. Chem. Soc. Jpn.* **45**, 2783 (1972); G. Piancatelli, A. Scettri, and M. D'Auria, *Tetrahedron Lett.*, 2199 (1977); 1507 (1979).

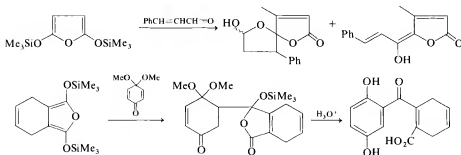
<sup>95</sup> P. Brownbridge and T.-H. Chan, *Tetrahedron Lett.* **21**, 3423, 3427, 3431 (1980).

Under the influence of titanium(IV) chloride, aldehydes and ketones react with a bisilyl ether at both the 3(4)-positions thus leading in a remarkably direct fashion into one of the major divisions of lignan chemistry (Scheme 21). Substituents at the 3(4)-positions direct the reaction to the 2(5)-positions, and both aldol condensations and Michael additions are possible, although only one insertion occurs. Among other products, 4-hydroxybutenolides can be made by this route (Scheme 22). The bisilyl ether provides an example of an umpolung for the acid anhydride grouping (Scheme 22). Quinones do not add to the ether; they oxidize it too easily and the products are a (silylated) quinol and a maleic anhydride derivative. Quinone acetals



SCHEME 21

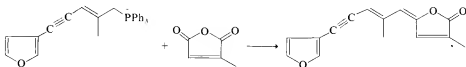
add easily, however, and the products offer an easy entry into anthraquinone chemistry (Scheme 22).<sup>95</sup>



SCHEME 22

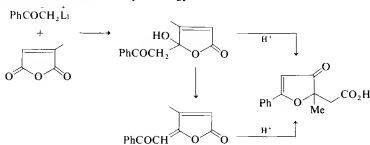
Furan-2,5-dione, or maleic anhydride, can quite reasonably be regarded as furanoquinone, the reduced form being furan-2,5-diol. The carbonyl groups do have some "ketonic" activity, and in Scheme 23 the key step of a second route to frelingyne (**86** in Vol. 30) makes use of this capacity in a reaction with another phosphorus ylide reagent.<sup>96</sup> (cf. Scheme 16). Even ordinary (carbonyl stabilized) carbanions will undergo such aldol con-

<sup>96</sup> A. P. Gara, R. A. Massey-Westropp, and G. D. Reynolds, *Tetrahedron Lett.*, 4171 (1969).



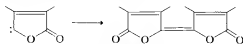
SCHEME 23

condensations with substituted furan-2,5-diones (Scheme 24) to form related 5-arylidenebutenolides.<sup>97</sup> Triethyl phosphite reduces 3,4-dimethyl furan-2,4-dione to a bifurandione; by analogy, an aldol condensation between the



SCHEME 24

anhydride and a reduced form, a furan-2(5H)-one, might be responsible, but Bird and Wong are probably correct in suggesting a carbene intermediate that dimerizes (Scheme 25).<sup>98</sup> In superacid solution, furan-2,5-dione is protonated on one of its carbonyl oxygen atoms.<sup>99</sup>



SCHEME 25

## B. FURAN-3-OL AND FURAN-3,4-DIOL

Studies of simple furan-3-ol derivatives are still sparse. The ketonic tautomers are better known in the sense that 2,2-disubstitution stabilizes them not only against isomerization but also against oxidation. These non-enolizable ketones are considered very briefly.

<sup>97</sup> G. M. Strunz and P. I. Kazindi, *Can. J. Chem.* **54**, 415 (1976).

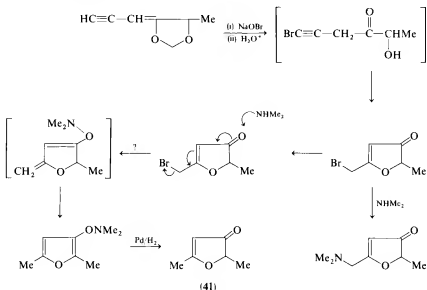
<sup>98</sup> C. W. Bird and D. Y. Wong, *Chem. Commun.*, 932 (1969).

<sup>99</sup> G. A. Olah, Y. K. Mo, and J. L. Grant, *J. Org. Chem.* **38**, 3207 (1973).



1. *Furan-3-ol*

Syntheses of 3-furanol bear strong family resemblances to several of the syntheses of other furans detailed in Section II (Vol. 30) where Scheme 13 shows a useful method based upon cyclization in a cumulene alcohol induced by *t*-butoxide ion in dimethyl sulfoxide solvent.<sup>99a</sup> The approach gives a furanone or a 3-methoxyfuran depending upon the substitution pattern, although 3-methoxyfuran derivatives are best made from 3-iodofurans by nucleophilic substitution with methoxide ion.<sup>100</sup> Cyclization in an acetylenic alcohol is described by Meister as a route to muscarines; the key stage is shown in Scheme 26 along with a most unusual reaction of the product with dimethylamine which partly replaces the bromine as expected but partly seems to mount a nucleophilic attack upon the carbonyl group at the "wrong" end, the oxygen atom.<sup>101</sup>



SCHEME 26

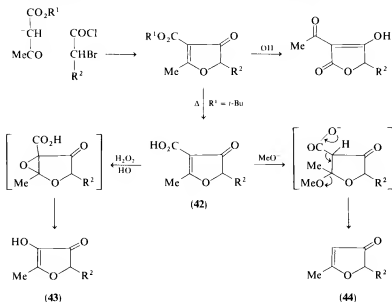
<sup>99a</sup> J. A. Rompes, S. Hoff, P. P. Montijn, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **88**, 1445 (1969); P. H. M. Schreurs, J. Meijer, P. Vermeer, and L. Brandsma, *Tetrahedron Lett.*, 2387 (1976).

<sup>100</sup> J. Srogl, M. Janda, and I. Stibor, *Collect. Czech. Chem. Commun.* **35**, 3478 (1970).

<sup>101</sup> H. Meister, *Justus Liebig's Ann. Chem.* **701**, 174 (1967); H. Meister and G. Peitscher, *ibid.*, 1908 (1974).

Another preparation of 2,5-dimethylfuran-3-ol (**41**) is included for its exceptional simplicity, even though it lacks versatility. Biacetyl (2,3-butanedione) dimerizes in alkali to form an aldol converted by acid to the desired product in yields rising 60%.<sup>102</sup> A very simple method has also been published for converting commercially available 2,3-dihydro-5-methylfuran to 5-methylfuran-3(2*H*)-one, tautomeric with 5-methylfuran-3-ol, by means of oxidation with selenium dioxide. According to the <sup>1</sup>H-NMR spectrum, the product is 80% ketone, 20% enol.<sup>103</sup> The furanone is produced when 2-deoxy-D-ribose is treated with acid.<sup>104</sup>

A method with considerable scope is a variation of the Feist-Benary synthesis using a 2-chloroacetyl chloride instead of a 2-chloroketone.<sup>105,106</sup> The main variation (Scheme 27) leads to acid **42** which can be epoxidized



SCHEME 27

and so transmuted into the 3,4-furandiols series (**43**) or simply decarboxylated to give the furanone (**44**). The decarboxylation gives bad results unless the

<sup>102</sup> C. Venturello and R. D'Aloiso, *Synthesis*, 754 (1977).

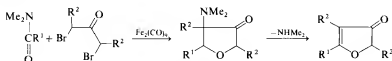
<sup>103</sup> D. V. Banthorpe and P. N. Christou, *Phytochemistry* **18**, 666 (1979).

<sup>104</sup> J. K. Seydel, E. R. Garrett, W. Diller, and K.-J. Schaper, *J. Pharm. Sci.* **56**, 858 (1967).

<sup>105</sup> R. Gelin, A. Galliaud, B. Chantegrel, and S. Gelin, *Bull. Soc. Chim. Fr.*, 1043 (1974); B. Chantegrel, D. Hartmann, and S. Gelin, *Tetrahedron* **33**, 45 (1977).

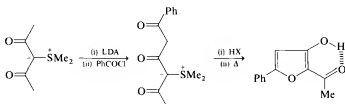
<sup>106</sup> D. de Rijke and H. Boelens, *Recl. Trav. Chim. Pays-Bas* **92**, 731 (1973).

somewhat unorthodox elimination method is used as indicated. Another variation shown leads into the tetrone acid (furan-2,4-diol) series. Compounds similar to the furanone (**44**) are responsible in part for the characteristic odors and flavors of various foodstuffs<sup>107</sup> such as coffee ( $R = \text{Me}$ )<sup>108</sup> and onion oils ( $R = n\text{-C}_6\text{H}_{13}$ ).<sup>109</sup> Some of these products are themselves versatile starting materials that react with amines, hydrazines, and similar reagents to supply a wide variety of nitrogen heterocycles valued for pharmacological reasons.<sup>105</sup> Another general synthesis has been aimed chiefly at the pharmacologically important muscarine analogs and is based upon the cycloaddition of an oxyallyl species to the carbonyl group of a dimethylamide (Scheme 28). Yields are 50% or better for simple alkyl or aryl derivatives.<sup>110,111</sup>



SCHEME 28

Acyl substituents or ester groups always help to stabilize electron-rich furan rings, and their presence assists synthesis. Stabilization of product is also seen in a route (Scheme 29) based upon sulfur ylide chemistry. The yield is nearly quantitative, and according to the NMR spectrum the com-



SCHEME 29

<sup>107</sup> G. Ohloff and I. Flament, *Prog. Chem. Org. Nat. Prod.* **36**, 231 (1979); G. Ohloff, *Fortschr. Chem. Forsch.* **12**, 185, 210 (1969).

<sup>108</sup> P. Friedel, V. Krampl, T. Rodford, J. A. Renner, F. W. Shepherd, and M. A. Gianturco, *J. Am. Food Chem.* **19**, 530 (1971).

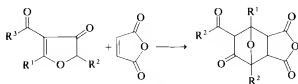
<sup>109</sup> H. Boelens, P. J. de Valois, H. J. Wobben, and A. van der Gen, *J. Am. Food Chem.* **19**, 984 (1971).

<sup>110</sup> M.-A. Barrow, A. C. Richards, R. H. Smithers, and H. M. R. Hoffmann, *Tetrahedron Lett.*, 3101 (1972).

<sup>111</sup> Y. Hayakawa, H. Takaya, S. Makino, K. Hayagawa, and R. Noyori, *Bull. Chem. Soc. Jpn.* **50**, 1900 (1977).

pound is mainly in the form of the enol shown and not the usual furanone form.<sup>112</sup>

As furanones (often the only form seen) 3-furanols absorb in the expected IR region near  $1700\text{ cm}^{-1}$  and are also responsible for ionization potentials near 9.2 eV in alkylated members of the series. The enol should be much easier to ionize, considering 3-methoxy-2,5-dimethylfuran succumbs at 7.85 eV.<sup>113</sup> Nevertheless, such compounds often behave chemically as heterocyclic phenols; thus, 2,5-dimethylfuran-3-ol couples at the 2-position with diazonium ions.<sup>114</sup> To avoid this kind of "ortho" substitution in the preparation of Mannich salts,<sup>115</sup> Hayagawa *et al.*<sup>111</sup> acetylate 2,4-dimethylfuran-3(2H)-one to obtain the enol acetate, after which formaldehyde and dimethylamine selectively attack the 5-position giving **45**. Acid hydrolysis removes the protective acetate group. A reaction very tempting to formulate as a cycloaddition to the furanol form of a furan-3-one occurs between furan-2,5-dione and the furanones of the general structure depicted in Scheme 30; of course, a stepwise sequence is equally possible and currently no distinguishing evidence is available. The products are found to have exo stereochemistry by NMR, and they epimerize readily at the  $\beta$ -diketonic methine position.<sup>116</sup> The reaction has actually long been known in a disguised form in which 1,3-dicarbonyl compounds condense with anhydrides to give oxabicycloheptenes.<sup>117</sup>



SCHEME 30

Those 3(2H)-furanones with a methylene group at the 2-position condense with ethyl formate and amines to give aminomethylene derivatives of type **46**. In such compounds the heterocyclic ring is easily opened by nucleophiles because the functional grouping is that of a vinylogous ester; with amines,

<sup>112</sup> M. Yamamoto, *J. C. S. Perkin I*, 1688 (1976).

<sup>113</sup> O. Thörstadi, K. Undheim, R. Lewitz, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 652 (1975).

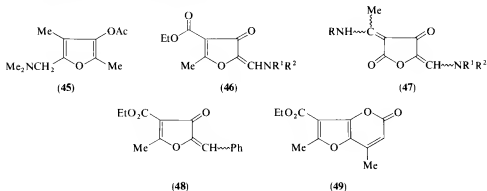
<sup>114</sup> C. Venturello and R. D'Aloisio, *Synthesis*, 283 (1979).

<sup>115</sup> J. V. Greenhill, P. H. B. Ingle, and M. Ramli, *J. C. S. Perkin I*, 1667 (1972).

<sup>116</sup> R. Gelin, S. Gelin, B. Chantegrel, A. Galliaud, and R. Dolmazon, *Bull. Soc. Chim. Fr.*, 2061 (1974).

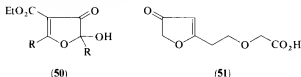
<sup>117</sup> E. Berner and P. Kolsaker, *Tetrahedron* **24**, 1199 (1968); R. D. Bailey and G. M. Sirunz, *Can. J. Chem.*, **44**, 2548 (1966); C. W. Bird and P. Molton, *Tetrahedron Lett.*, 1891 (1966).

for example, the ring opens, closes in the alternative direction, and is then converted to an enamine of type **47** belonging to the furan-2,4-diol series.<sup>105,118</sup> Such furanones also condense readily with aromatic aldehydes; the products (**48**) have had configurations assigned<sup>119</sup> and have been very extensively used by Gelin *et al.*<sup>105,120</sup> to prepare numerous pyrazoles and other nitrogen heterocyclic compounds. In alkali the dihydroderivatives are transformed into tetrionic acids (see part C below).<sup>121</sup> Again the sensitivity of the ring to nucleophiles is evident. Yet the ring is stable to acids, and furanones containing it condense with ethyl acetoacetate just as phenols do and give 2-pyrones such as **49**.<sup>105</sup>



Furan-3-ones are easily oxidized. In alkali, air attacks them giving  $\alpha$ -ketols that are also cyclic hemiacetals (**50**) acidic enough to form salts with hydrogen carbonate ion. Acetylation is normal; acetates can be obtained directly by oxidizing the furanones with lead(IV) acetate.<sup>105,122</sup>

Enolizable 3(2H)-furanones are very rarely found in plants. Oospolide, a metabolite of *Oospora astringens*, has structure **51** and is not a medium-



<sup>118</sup> B. Chantegrel and S. Gelin, *J. Heterocycl. Chem.* **16**, 1335 (1979).

<sup>119</sup> I. da Rocha Pitta, M. do Socorro Lucerda, and C. L. Duc, *J. Heterocycl. Chem.* **16**, 821 (1979).

<sup>120</sup> S. Gelin and D. Hartmann, *Synthesis*, 186 (1977); S. Gelin and M. Chabannet, *ibid.*, 448 (1978); S. Gelin, R. Gelin, and D. Hartmann, *J. Org. Chem.* **43**, 2665 (1978); B. Chantegrel, *J. Chem. Res., Synop.*, 127 (1977); B. Chantegrel and S. Gelin, *J. Heterocycl. Chem.* **14**, 155 (1978).

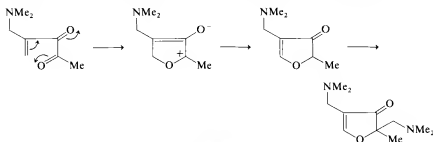
<sup>121</sup> S. Gelin and R. Gelin, *J. Heterocycl. Chem.* **15**, 327 (1978).

<sup>122</sup> S. Gelin and R. Gelin, *J. Heterocycl. Chem.* **14**, 75 (1977).

ring lactone as thought originally.<sup>123</sup> The confusion arose precisely because of the sensitivity of the furanone ring to alkaline hydrolysis.

## 2. Nonenolizable 3 (2H)-Furanones

Several routes include oxyallyl cycloadditions,<sup>110,111</sup> cyclizations of unsaturated alcohols or enols,<sup>99a,124</sup> the use of 1,3-dithian as a carbanionic focal point for assembling the parts to make the heterocyclic ring,<sup>125</sup> and the condensation of cyclic sulfonium ylides with diketene to give spiro-furanones.<sup>126</sup> Biacetyl (2,3-butanedione) reacts twice at one methyl group in the formation of a Mannich base capable of an unusual cyclization sketched in Scheme 31; the furanone then undergoes another Mannich reaction.<sup>115</sup> The possibility is interesting despite its lack of generality.



SCHEME 31

The reaction between the acid chloride of chromone-2-carboxylic acid and ethyl ethoxymagnesiocetoacetate probably leads to the expected  $\beta$ -diketone which enolizes and cyclizes spontaneously to spirofuranone (**52**).<sup>127</sup> A different approach was made by Hungarian workers in their synthesis of tachrosin (**53**), an unusual kind of flavone isolated from *Tephrosia polystachyoides* and one of the earliest natural furanones to be isolated. They subjected an unsaturated ketone (Scheme 32) to oxidative rearrangement by thallium(III) salts, a reaction well known in chalcone chemistry, and eliminated methanol from the product to obtain the necessary starting material.<sup>128</sup>

<sup>123</sup> K. Nitta, Y. Yamamoto, and Y. Tsuda, *Tetrahedron Lett.*, 4231 (1968).

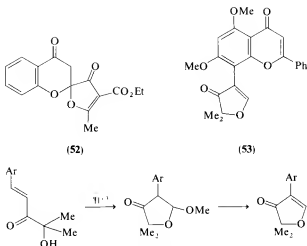
<sup>124</sup> P. K. Gupta, J. G. L. Jones, and E. Caspi, *J. Org. Chem.* **40**, 1420 (1975); W. Reid and A. Marhold, *Chem. Ber.* **107**, 1714 (1974); M. Ito, M. Ohno, E. Takano, Y. Oda, and K. Tsukida, *Heterocycles*, 1553 (1979).

<sup>125</sup> F. Sher, J. L. Isidor, H. R. Taneja, and R. M. Carlson, *Tetrahedron Lett.*, 577 (1973).

<sup>126</sup> T. Mukaiyama, M. Higo, and T. Sakashita, *Tetrahedron Lett.*, 3697 (1971).

<sup>127</sup> R. C. Brown and H. Cairns, *J. C. S. Perkin I*, 1553 (1976).

<sup>128</sup> S. Antus, L. Farkas, M. Nogradi, and F. Boros, *J. C. S. Perkin I*, 948 (1977).



SCHEME 32

Other naturally occurring 3(2*H*)-furanones are known, including jatrophone,<sup>129</sup> zexbrevin,<sup>130</sup> and geiparvarin,<sup>131</sup> which has been synthesised as part of a program devoted to 3(2*H*)-furanones because of their marked antitumor activity<sup>132</sup>; pseurotin is an unusual spiro-3-furanone obtained from a fungal source *Pseudorotium ovalis* Stolk (Ascomycetes).<sup>133</sup> A review is available.<sup>134</sup>

### 3. Furan-3,4-diol

The dione (54) has been compared with the carbocyclic and sulfur heterocyclic analogs.<sup>135</sup> In striking contrast to these, it shows no tendency to enolize, and the <sup>1</sup>H-NMR spectrum consists of a singlet at  $\delta$  4.49. Yet enolization should remove the repulsion between the aligned carbonyl groups

<sup>129</sup> S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.* **98**, 2295 (1976).

<sup>130</sup> A. R. de Vivar, C. Guerrero, E. Diaz, and A. Ortega, *Tetrahedron* **26**, 1657 (1970).

<sup>131</sup> F. N. Lahey and J. K. Macleod, *Aust. J. Chem.* **20**, 1943 (1967); J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 237 (1972); A. B. Smith and P. J. Jerris, *Tetrahedron Lett.*, 21, 711 (1980); *Synth. Commun.* **8**, 421 (1978), A. B. Smith and R. M. Scarborough, *Tetrahedron Lett.*, 4193 (1978).

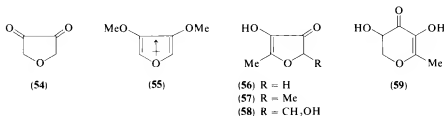
<sup>132</sup> K. Padmawinata, *Acta Pharm.* **4**, 1 (1973).

<sup>133</sup> P. Block, C. Tamm, P. Bollinger, T. J. Petcher, and H. P. Weber, *Helv. Chim. Acta* **59**, 133 (1976).

<sup>134</sup> N. H. Fischer, E. J. Olivier, and H. D. Fischer, *Prog. Chem. Org. Nat. Prod.* **38**, 47 (1980).

<sup>135</sup> P. X. Iten, A. A. Hofmann, and C. H. Eugster, *Helv. Chim. Acta* **61**, 430 (1978).

and introduce delocalization energy. Whatever the explanation the diol remains unknown except as its ethers or as derivatives containing some additional factor stabilizing the enolic form. Mono enols are sometimes detected but no specific study seems to have been made although members of this series are now of considerable commercial importance as odiferous principles.<sup>107</sup> Here we shall first discuss the extensive studies made by Eugster and his associates of the chemistry of 3,4-dimethoxyfuran (**55**). New descriptions of the preparation of this compound<sup>85,135</sup> and 3,4-dibenzyl-oxyfuran are available.<sup>135</sup>



Calculations (PPP and CNDO) point to enhanced negative charge at the 2(5)-position and a dipole moment (**55**) inverse to that in unsubstituted furan; nevertheless, both mono- and dilithiation occur readily at the  $\alpha$ -positions as usual and so does the formation of Mannich bases with formaldehyde and dimethylamine.<sup>135</sup> Standard methods produce from these derivatives a wide variety of others.

The dimethoxyfuran is very nucleophilic and reacts with diazonium salts in pyridine as shown in Scheme 33. The pyridine residue is easily displaced by thiols or alcohols, opening a wide range of possibilities.<sup>136</sup> More attention seems to have been paid to cycloadditions, however, since a 3(4)-methoxyl group assists the reaction with dienophiles. An example was quoted earlier (see Scheme 12). The addition of acetylene diesters is known<sup>137</sup>; furan-2,5-dione and its monomethyl derivative add, but the dimethyl derivative does not,<sup>138</sup> nor does styrene.<sup>85</sup> One activating group may be enough, as in additions of nitrostyrenes and propiolic esters.<sup>85</sup> With furan-2,5-dione the exo and endo isomers are thought to be formed at about the same rate (unlike the situation in the parent furan), but the exo isomer is still the thermodynamically more stable.<sup>138</sup> A number of these reactions have been used to produce polymethoxyphenols and other compounds without, however,

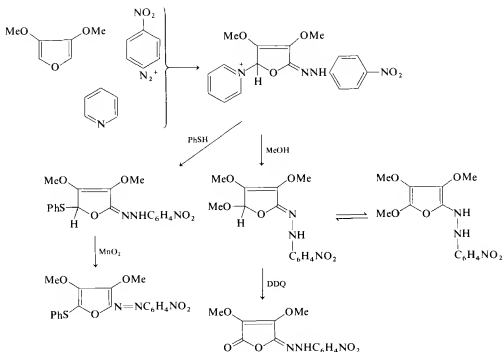
<sup>135a</sup> E. C. Kendall and Z. C. Hajos, *J. Am. Chem. Soc.* **82**, 3219, 3220 (1960); M. W. Miller, *Tetrahedron Lett.*, 2545 (1969).

<sup>136</sup> P. X. Iten and C. H. Eugster, *Helv. Chim. Acta* **61**, 1033 (1978).

<sup>137</sup> P. X. Iten and C. H. Eugster, *Helv. Chim. Acta* **61**, 1134 (1978).

<sup>138</sup> P. X. Iten, A. A. Hofmann, and C. H. Eugster, *Helv. Chim. Acta* **62**, 2202 (1979).





SCHEME 33

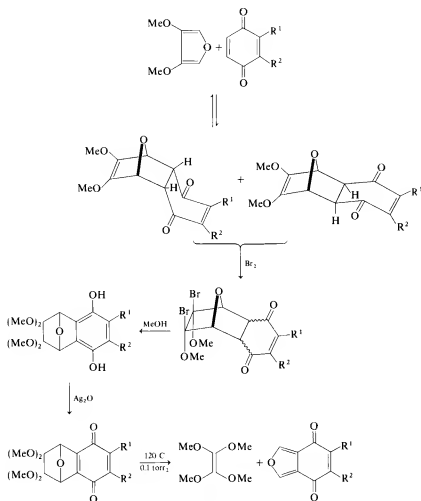
introducing any feature not already discussed. Worth a special note is the synthesis of isobenzofuran quinones by the method sketched in Scheme 34. Eugster and his colleagues discovered that the addition of the furan is controlled stereochemically by substituents  $R^1$  and  $R^2$  as usual and also, most remarkably, that the addition of halogen is specifically both *cis* and *exo*. There is no obvious explanation.<sup>139</sup>

Furan-3,4-diol derivatives are often written in the monoenolic form which is believed to be the parent nucleus of several important compounds responsible for the flavorings of various foodstuffs. The 2(5)-methyl derivative (56) has been detected in both soy sauce<sup>140</sup> and beef broth.<sup>141</sup> Related compounds occur in coffee and onion. The chief member of the series, furaneol (57), has a fruity flavor when dilute, changing to caramel as the concentration increases.<sup>107</sup> The substance isolated from the nonenzymatic "browning" of

<sup>139</sup> A. A. Hofmann, I. Wyrach-Walraf, P. X. Iten, and C. H. Eugster, *Helv. Chim. Acta* **62**, 2211 (1979).

<sup>140</sup> N. Nunomura, M. Sasaki, and T. Yokotsuka, *Agric. Biol. Chem.* **43**, 1361 (1979).

<sup>141</sup> C. H. Tonsbeek, A. J. Plancken, and T. von der Weerdhof, *J. Agric. Food Chem.* **16**, 1016 (1968).



SCHEME 34

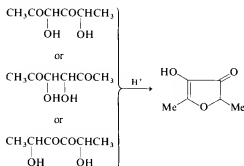
orange juice is not the furan (58) but the isomeric pyran derivative (59). Similarly, the substance obtained by treating glucose or fructose with amines in acetic acid is also a pyran and not a furan.<sup>142</sup> Among facts that enabled the revision to be made was the lack in the pyran of any long range coupling to the methyl protons such as is known to occur in the furanone (57) between the 5-methyl group and the C-2 hydrogen atom.<sup>143</sup> Confirmation of the

<sup>142</sup> F. D. Mills, D. Weisleder, and J. E. Hodge, *Tetrahedron Lett.*, 1243 (1970).

<sup>143</sup> A. Hoffman, W. von Philipsborn, and C. H. Eugster, *Helv. Chim. Acta* **48**, 1322 (1965).

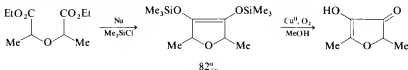
pyran nucleus was achieved by synthesis from the pyrone maltol.<sup>142</sup> Despite that revision, some still consider that sugars can under some circumstances yield furanoid flavor constituents. Japanese workers record an 88% yield of **56** from 6-deoxyglucose heated in ethanol with piperidine and acetic acid for 24 hr,<sup>144</sup> corresponding to the long-established conversion of rhamnose to furaneol. A prenyl-substituted member of the series is formed when the hop constituent, humulone, is heated with aqueous acid.<sup>145</sup>

The importance of such organoleptic compounds has evoked a number of synthetic routes capable of exploitation. All have the same aim, to obtain an acyclic dihydroxydione and induce cyclization and dehydration. The routes differ only in that they employ various tautomeric forms (Scheme 35).<sup>106,146-149</sup> The cyclization is achieved with acid; amberlite resin is also



SCHEME 35

successful.<sup>149</sup> Another approach, summarized in Scheme 36, is based on hydrofuran chemistry.<sup>150</sup>



SCHEME 36

<sup>144</sup> M. Matsui, T. Ogawa, and K. Takagi, *CA* **91**, 20309 (1979). *Jpn. Kokai Tokkyo Koho* 79,19,962 (1979).

<sup>145</sup> L. De Taeye, D. De Keukeleire, and M. Verzele, *Bull. Soc. Chim. Belg.* **88**, 87 (1979).

<sup>146</sup> G. A. M. Ouweland and S. B. Tjan, *Recl. Trav. Chim. Pays-Bas* **93**, 312 (1974).

<sup>147</sup> L. Re, B. Maurer, and G. Ohloff, *Helv. Chim. Acta* **56**, 1882 (1973).

<sup>148</sup> G. Buchi, E. Demole, and A. F. Thomas, *J. Org. Chem.* **38**, 123 (1973).

<sup>149</sup> B. Bianani, V. Caciagli, and G. E. Bianchi, *Ger. Offen.* 2,845,843.

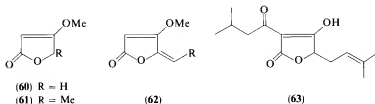
<sup>150</sup> M. Matsui, T. Ogawa, T. Kitahara, and K. Takagi, *CA* **92**, 110828 (1989). *Jpn. Kokai Tokkyo Koho* 79 115,369 (1979).

## C. FURAN-2,4-DIOL: TETRONIC ACIDS

There has been almost no activity in connection with true furans of this class which are almost unknown. Recent attempts to prepare 2,4-dimethoxyfuran were fruitless.<sup>85</sup> Lithiation of 4-methoxyfuran-2(5*H*)-one (**60**) produces the 5-anion normally, but this reacts only at carbon giving with iodomethane the homolog (**61**) and with aldehydes a variety of 5-ylidenefuranones (**62**). No enol ether is formed. Whereas this is not remarkable, the failure of acetylation and particularly silylation procedures to furnish enol derivatives is almost unprecedented.<sup>85</sup> The situation is not yet understood.

In striking contrast, the tautomeric grouping 4-hydroxy-2(5*H*)-furanone (commonly known as tetronic acid) is the characteristic unit in a large number of sponge, fungal, and lichen metabolites. The class includes some important pigments and some compounds with substantial biological activity; it has also provided a prime target for biosynthetic studies. Indeed, these compounds form a large, important class that have been reviewed extensively.<sup>72,73</sup> This section is therefore largely confined to work published since 1975.

Tautomerism in the tetronic acid nucleus concerns only the vinylogous acid and never includes the methylene group [but note obtusifolin (**127**)]. Two isomers have been detected in 2-acylated tetronic acids<sup>150a</sup> (**63**) that are



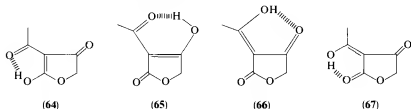
produced by the autoxidation of hop constituents, thus affecting the flavor of beer. Furan derivatives, especially furfural, are thought to introduce a "cardboard" taste.<sup>151</sup> A more detailed study of 2-acyltetronic acid tautomerism has been made possible by <sup>13</sup>C-NMR spectroscopy because this technique reveals distinctions between ketonic and lactonic carbon and between these and enol carbon. The analysis supports the view that of the four tautomers of 2-acetyltetronic acid, **64** is unimportant in a mixture consisting of about equal amounts of tautomers **65** and **66**<sup>151a</sup> with rather less

<sup>150a</sup> Like butenolides, tetronic acids when so named are numbered from the carbonyl position, not from the ring oxygen atom.

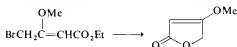
<sup>151</sup> D. De Keukeleire, L. DeTaele, and M. Verzele, *Tetrahedron* **32**, 2923 (1976).

<sup>151a</sup> Only one set of signals is seen for each of these; it is unclear whether there is a rapid interconversion, leading to averaging, or a single structure.

67.<sup>152</sup> In contrast, 4-benzylidenetetrone exists as only a single tautomer.<sup>152</sup> Simple tetrone acids are always written as 4-hydroxyfuran-2(5H)-ones even when there is little doubt that 2-hydroxyfuran-4(4H)-one tautomers are also present. Diazomethane affords the methyl ethers of both,<sup>153</sup> and 2-alkoxyfuranones are readily available from the copper-catalyzed decomposition of malonate ester diazoketones.<sup>152,154</sup>



Whereas methods of synthesising tetrone acids are plentiful, no one method has received general approval. The simplest tetrone acids have been the hardest to prepare readily in reasonable quantity. Zimmer *et al.*<sup>155</sup> have revived Kummel's method for the preparation of tetrone acid itself, the cyclization of  $\alpha,\gamma$ -dibromoacetoacetic ester being achieved simply by heat. A similar and very effective cyclization (Scheme 37) of a brominated enol



SCHEME 37

ether of acetoacetate is catalyzed by zinc bromide in a direct route to the methyl tetronate used by Pelter *et al.*<sup>156</sup> as the starting point for the elaboration of more complex compounds. Another related cyclization is shown in Scheme 38; it is said to require exactly 100% sulfuric acid for success and it gives what can be regarded as acid bromides of the tetrone series although their hydrolysis has not yet been reported.<sup>157</sup> Such bromocompounds

<sup>152</sup> S. Gelin and P. Pollet, *Tetrahedron Lett.*, **21**, 4491 (1980).

<sup>153</sup> I. Rothberg and P. Shubiak, *Tetrahedron Lett.*, 769 (1975); G. Cimino, S. De Stefano, L. Minale, and E. Fattorusso, *Tetrahedron* **28**, 333 (1972); E. Cafieri, E. Fattorusso, C. Santacroce, and L. Minale, *ibid.*, 1579.

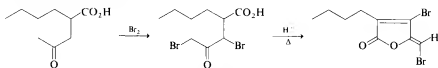
<sup>154</sup> S. Bien and A. Gillon, *Tetrahedron Lett.*, 3073 (1974).

<sup>155</sup> H. Zimmer, W. W. Hillstrom, J. C. Schmidt, P. D. Seemuth, and R. Vogli, *J. Org. Chem.* **43**, 1541 (1978).

<sup>156</sup> A. Pelter, M. T. Ayoub, J. Schultz, R. Hansel, and D. Reinhardt, *Tetrahedron Lett.*, 1627 (1979).

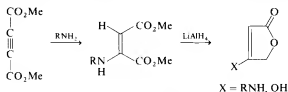
<sup>157</sup> C. M. Beechan and J. J. Sims, *Tetrahedron Lett.*, 1649 (1979).

occur in the red seaweed, *Delisea fimbriata* (Bonnemaisoniaceae), the one shown being fimbrolide.



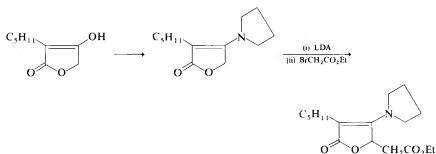
SCHEME 38

Greenhill and Tomassini<sup>158</sup> introduced an exceptionally simple tetronic acid synthesis from methyl but-2-ynoate (Scheme 39). It contains features



SCHEME 39

that have proved valuable in more recent work by Holker and his colleagues in which the enamines (tetronic amides) are produced by interaction of the enol ether with pyrrolidine with azeotropic distillation of methanol. The lactone is not affected. Lithium diisopropylamide converts the enamine smoothly to the tetronic 4-carbanion for alkylation and other purposes, and the substituted enamine is then readily hydrolyzed to regenerate the tetronic acid nucleus (Scheme 40).<sup>159</sup> One particular advantage of the method lies in this easy hydrolysis, the corresponding hydrolysis of ethers, though possible,



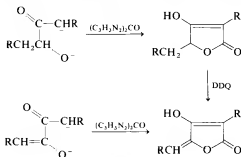
SCHEME 40

<sup>158</sup> J. V. Greenhill and T. Tomassini, *Tetrahedron Lett.*, 2683 (1974).

<sup>159</sup> S. C. M. Fell, J. Heaps, and J. S. E. Holker, *J. C. S. Chem. Commun.*, 81 (1979).

being relatively erratic. Multicolanic acid, a metabolite of *Penicillium multicolor*, and similar compounds have been obtained in a like manner.<sup>159</sup>

When a suitable  $\alpha$ -ketol is accessible it can be converted by amide reagents to its dianion and condensed with 1,1'-carbonyldiimidazole; this constitutes a direct insertion of a carbonyl group and offers a versatile way of reaching the tetrone system, although yields are only moderate (Scheme 41).<sup>160</sup> The



SCHEME 41

same sequence beginning with an  $\alpha$ -diketone affords unsaturated analog (pulvinone, if R is 4-MeOC<sub>6</sub>H<sub>4</sub>), and in one example DDQ oxidation provided an alternative route.<sup>160</sup> Older methods have been refurbished; for example, one has been improved by redesigning it with sulfur carbanion and thioester components and it now provides very good yields.<sup>161</sup> Another has been improved (although the conditions remain critical) by the use of the magnesium derivative of malonic half ester.<sup>162</sup> Bloomer and Kappler<sup>163</sup> used established methods to convert (*S*)-malate to carlosic acid (**68**) thus enabling them to establish the absolute configuration of this fungal product.

Cyclizations giving tetrone acids under basic conditions are possible but rare. One example occurs in a recent synthesis of piperolide (Scheme 42) that also features a DDQ oxidation;<sup>164</sup> another is mentioned below.

Extensive studies on the synthesis of 4-ylidenetetrone acids conducted by Pattenden and his colleagues have been based mainly upon furan-2,5-diones (maleic anhydrides) in which a carbonyl reacts selectively. Unexpectedly, metal hydride attacks both carbonyl groups about equally in the methyl derivative, but in the methoxyfuran-2,5-diones, where electron release from the methoxy group greatly reduces the activity of the distal carbonyl group,

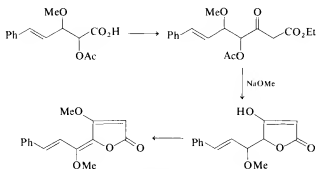
<sup>160</sup> P. J. Jerris, P. M. Wovkulich, and A. B. Smith, *Tetrahedron Lett.*, 4517 (1979).

<sup>161</sup> R. E. Damon, T. Luo, and R. H. Schlessinger, *Tetrahedron Lett.*, 2749 (1976).

<sup>162</sup> P. Pollet and S. Gelin, *Tetrahedron* **34**, 1453 (1978).

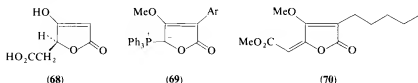
<sup>163</sup> J. L. Bloomer and F. E. Kappler, *J. Org. Chem.* **39**, 113 (1974).

<sup>164</sup> H. Achenbach and J. Witzke, *Tetrahedron Lett.*, 1479 (1979).



SCHEME 42

it is mainly the other group that is affected.<sup>165</sup> For this reason butenolides are easily available for bromination and conversion to phosphoranes (**69**) and so to compounds like the pulvinones<sup>165,165a</sup> (cf. Ref. 156). A more efficient alternative, however, is to allow the anhydrides to react selectively with phosphoranes to give 5-ylidene compounds directly, as in a synthesis of (*E*)-*O*-methylmulticolanate (**70**), from a furan-2,5-dione in conjunction with



an ester phosphorane. In such syntheses the (*E*)-isomer is the main product although both are formed. Natural products in this series all have the (*E*)-configuration, as shown by X-ray methods in combination with 5-methine <sup>1</sup>H-NMR bands very close to  $\delta$  5.83. The *Z* isomers have a signal at  $\delta$  5.63, and the downfield shift is attributed to some influence of the heterocyclic oxygen atom.<sup>166</sup>

Like other butenolides, tetronic esters (ethers) will also form 4-carbanions with lithiating agents and react with carbonyl compounds to give 4-ylidene derivatives. Scheme 43 (Path A) outlines this approach to a synthesis of the *O*-methyl ether of pinastric acid, a partial solvolysis product of a lichen bilactone in the vulpinic acid series.<sup>166a</sup> Gomphidic acid has been synthesised similarly. The most troublesome feature of this route is the dehydration, which requires stringent conditions (P<sub>2</sub>O<sub>5</sub> in benzene<sup>165</sup> or sublimation<sup>159</sup>).

<sup>165</sup> D. W. Knight and G. Pattenden, *J. C. S. Perkin I*, 62, 70 (1979).

<sup>165a</sup> Pulvinones are derivatives of 4-benzylidene-2-phenyltetronic acid.

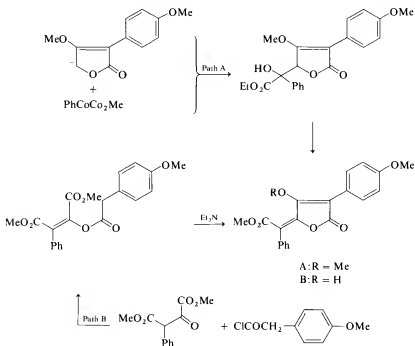
<sup>166</sup> M. J. Begley, D. R. Gedge, and G. Pattenden, *J. C. S. Perkin I*, 89 (1979).

<sup>166a</sup> D. W. Knight and G. Pattenden, *J. C. S. Perkin I*, 84 (1979).



Weinstock *et al.*<sup>167</sup> have devised a route in which the double bond is provided at an earlier, easier stage (Scheme 43, Path B) and found that the geometry is again that desired, as shown by NMR and IR methods. None of the older synthetic methods were definitive, and even recent ones have not been rigorously unequivocal.<sup>167</sup> Definitive syntheses of prenyl and chroman derivatives of aryltetronic acids have also assisted the elucidation of the way in which aspulvinone (71) is built up by *Aspergillus terreus*. The nucleus is probably first monoprenylated and then converted to the mixed prenylated phenol-chroman system before the dichroman is reached.<sup>168</sup> An easy thermal rearrangement has long been known to be characteristic of 4-arylidene tetronic acids and has resulted in wrong structures being allocated to certain pulvinones; Begley *et al.*<sup>168</sup> correcting such assignments by X-ray diffraction studies.

In a major study of the biosynthesis of multicolic acid from acetate by *Penicillium multicolor*, Gudgeon, Holker, and Simpson made excellent use

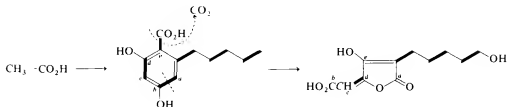


SCHEME 43

<sup>167</sup> J. Weinstock, J. E. Blank, H.-J. Oh, and B. M. Sutton, *J. Org. Chem.* **44**, 673 (1979).

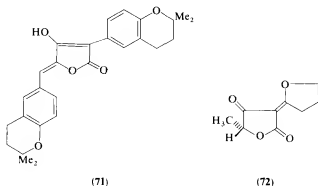
<sup>168</sup> M. J. Begley, D. W. Knight, and G. Pattenden, *Tetrahedron Lett.*, 131 (1976); *J. C. S. Chem. Commun.*, 717 (1975).

of isotopic labeling and  $^{13}\text{C}$ -NMR spectrometry, utilizing  $^{13}\text{CH}_3\text{CO}_2\text{H}$ ,  $\text{CH}_3^{13}\text{CO}_2$ , and  $^{13}\text{CH}_3^{13}\text{CO}_2\text{H}$  to assign carbon atoms for the transformation shown in Scheme 44. The report contains much useful NMR information on tetrone acids and includes details of lanthanide-induced shifts in which the alcohol function is the coordination site.<sup>169</sup>



SCHEME 44

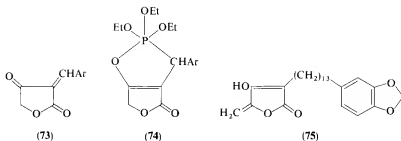
Following the discovery that carolic acid exists in trichloromethane solution as the cyclic anhydride in a mixture of geometrical isomers, it has been shown that the compound crystallizes from ethanol as the (*E*)-isomer (72).



The system is very sensitive to traces of acid or to light. The  $^{13}\text{C}$ -NMR spectra show the equilibrium to be solvent dependent. Terrestric acid and carlic acid behave similarly.<sup>170</sup> Evidently, the butenolide ring system is entirely compatible with an exo double bond at its 2-position, and accordingly the condensation of tetrone acid itself with aromatic aldehydes readily affords 3-arylidene-furandiones (73) as mixtures of two geometric isomers.<sup>155</sup> The similar condensation with 4-hydroxycoumarin is better known but

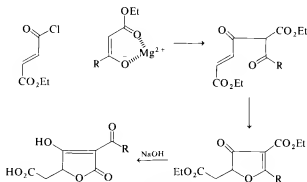
<sup>169</sup> J. A. Gudgeon, J. S. E. Holker, and T. J. Simpson, *J. C. S. Chem. Commun.*, 636 (1974).

<sup>170</sup> J. P. Jacobsen, T. Reffstrup, R. E. Cox, J. S. E. Holker, and P. M. Boll, *Tetrahedron Lett.*, 1081 (1978).



leads instead to arylidenbispyrones with no exocyclic double bond; dimedone behaves similarly. The 2-arylidene-tetronic acids add triethyl phosphate(III) smoothly, the products being oxaphospholes (74).<sup>155</sup>

The 2-acylation of tetronic acids is important because many natural products might be obtained, but a wholly satisfactory acylation is unavailable. Some newer attempts include the use of thallium(I) salts and acyl fluorides (they fail) or acyl chlorides (they merely give esters).<sup>163</sup> The Fries reaction with esters and tin(IV) chloride as catalyst is sometimes successful<sup>171</sup>; and when it is not, a direct acylation of the tetronic acid with an acyl chloride and titanium(IV) chloride may work.<sup>163</sup> An earlier method by Haynes and Jamieson in which an acetate is heated with phosphoric acid in toluene to produce a 2-acetyltetronic acid has been revived and generalized.<sup>172</sup> Svendsen and Boll<sup>173</sup> avoid the problem by preparing a furanone ester (cf. Scheme 43, Path B) and causing the ring and side-chain groups to exchange places under the influence of alkali (Scheme 45). They have synthesized carlosic,



SCHEME 45

<sup>171</sup> F. H. Anderson, A. Svendsen, and P. M. Boll, *Acta Chem. Scand.* **28**, 130 (1974).

<sup>172</sup> J. Lehmann and H. Warnhoff, *Justus Liebigs Ann. Chem.*, 1287 (1974).

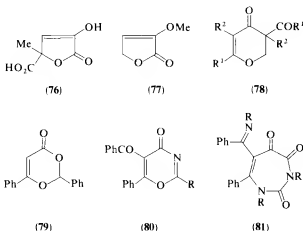
<sup>173</sup> A. Svendsen and P. M. Boll, *Tetrahedron Lett.*, 2821 (1974); *J. Org. Chem.* **40**, 1927 (1975).

viridicatic, and carlic acids in this manner. Tetronic acid derivatives such as viyelliptin (75) occur in the higher plants (Myristicaceae)<sup>174</sup>; their special features have not yet been the center of any close examination and they have not been synthesized. Fungi have supplied a number of 2-acyltetronic esters (ethers).<sup>175</sup>

#### D. FURAN-2,3-DIOL AND FURANTRIOLS

##### 1. *Furan-2,3-diol*

Until recently, zymonic acid was the only noteworthy member of this class, although that fact was concealed by incorrect structures until the correct one (76) was announced in 1970 by Bloomer and his associates.<sup>176</sup> However, the compound has been discovered not to be a natural product after all, but an artifact produced by the self-condensation of the pyruvic acid commonly present in certain culture fluids.



2,3-Dimethoxyfuran is prepared *in situ* for cycloadditions to activated acetylenes; the adducts are again useful sources of polyphenolic compounds.<sup>85</sup> Ketonic forms are usual. The bog asphodel contains the methyl ether (77), along with triol analogs considered below.<sup>177</sup> Similar lactones are

<sup>174</sup> O. R. Gottlieb, *J. Ethnopharmacol.* **1**, 309 (1979).

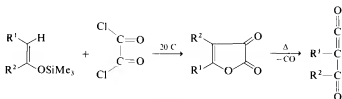
<sup>175</sup> K. Kobayashi and T. Ui, *Tetrahedron Lett.*, 4119 (1975).

<sup>176</sup> J. L. Bloomer, M. A. Gross, F. E. Kappler, and G. N. Pandey, *Chem. Commun.*, 1029 (1970).

<sup>177</sup> R. Tschesche and H.-J. Hoppe, *Chem. Ber.* **104**, 3573 (1971).

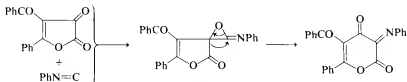
important as component parts of cephalosporin antibiotics, and an older, general synthesis has recently been greatly improved merely by using acid instead of the traditional alkaline hydrolysis at an intermediate stage.<sup>178</sup>

In fact the "quinones" are better known in this series. A general method for the preparation of furan-2,3-diones has been described as outlined in Scheme 46.<sup>179</sup> They have carbonyl bands above  $1800\text{ cm}^{-1}$  in the IR region.



SCHEME 46

The same work included an examination of spectral characteristics and disclosed that in the mass spectrum the main feature is a fragment formed by the loss of CO. The lactone carbonyl group is lost on heating, leaving an intermediate that dimerizes to the pyrone derivative (78).<sup>179</sup> The intermediate, which is probably a ketene (Scheme 46), can also be trapped in a variety of ways; benzaldehyde gives the 1,3-dioxinone (79) in 91% yield,<sup>180</sup> nitriles give the oxazinones (80),<sup>181</sup> carbodiimides the diazepinones (81),<sup>182</sup> and cyanates the corresponding pyrrolidones.<sup>182</sup> Sometimes other kinds of reactions occur. Isocyanides yield pyroneimines, the structures being confirmed by X-ray diffraction (Scheme 47).<sup>183</sup> At low temperatures (boiling toluene) the reaction with 2-aminophenol is merely amide formation, but at  $160\text{--}170^\circ\text{C}$  the product, a benzoxazine derivative, is again formed by loss of CO.<sup>184</sup>



SCHEME 47

<sup>178</sup> E. Galantay, C. Hoffman, and N. Paoella, *J. Org. Chem.*, **35**, 4277 (1970).

<sup>179</sup> S. Mural, K. Haegawa, and N. Sonada, *Angew. Chem., Int. Ed. Engl.*, **14**, 636 (1975).

<sup>180</sup> Yu. S. Andreichikov, L. F. Gein, and V. L. Gein, *Khim. Geterotsikl. Soedin.*, 1280 (1979).

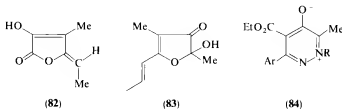
<sup>181</sup> E. Ziegler, C. Kollenz, C. Kriewitz, and W. Ott, *Justus Liebigs Ann. Chem.*, 1751 (1967).

<sup>182</sup> G. Kollenz, E. Ziegler, H. Igel, and C. Labes, *Chem. Ber.*, **109**, 2503 (1976).

<sup>183</sup> E. Ziegler, G. Kollenz, and W. Ott, *Justus Liebigs Ann. Chem.*, 2071 (1976).

<sup>184</sup> Yu. S. Andreichikov, L. A. Voronova, and A. V. Milyitin, *Zh. Org. Khim.*, **15**, 847 (1979).

In this series of furanones there are few known 5-ylidene derivatives. In his study of amino acid antagonists, Trowitzsch synthesized **82** by condensing 3-pentanone with ethyl oxalate and cyclizing the product. The external methyl group was shown to be *cis* to the ring oxygen atom by means of aromatic solvent-induced shifts. The compound had already been recognized as an active organoleptic constituent of some foods and as an antibiotic.<sup>185</sup>



For a minor constituent of *Stemphylium radicinum*, structure **83** has been deduced by Grove.<sup>186</sup> After saturation of the side chain over palladium the compound showed signs of ring chain tautomerism with 4-methyloctan-2,3,5-trione, which may have been formed by air oxidation of the furan-3-one (Section III.B.1). Such acidic ketols give salts with hydrogen carbonate ion but give acetates normally. The acetates are also obtainable by oxidizing the furan-3-one with lead(IV) acetate.<sup>105,121</sup> Ethers are available by the usual acid/alcohol treatment.<sup>121</sup> Gelin lists numerous examples along with spectroscopic data and has found that amines replace the ring oxygen atom, thus giving similar compounds in the pyrrole series.<sup>187</sup> The most interesting reaction is with hydrazines, for the products are pyridazinum oxides (**84**), a little studied system.<sup>188</sup> The presence of an ester substituent at position 4 enhances nucleophilic attack at position 5, and hydrazines then smoothly afford pyrazoles and pyrazines.<sup>189</sup>

## 2. Furantriols

Here we begin to encroach upon carbohydrate chemistry, especially with ascorbic acid, the most important member of the class. However, the reader should refer to Berger's study, which includes details of <sup>13</sup>C-NMR spectra, a discussion of how the pH dependence is determined by the various protonation sites, and details of the transition of the "quinone," dehydroascorbic

<sup>185</sup> W. Trowitzsch, *Justus Liebigs Ann. Chem.*, 1707 (1977).

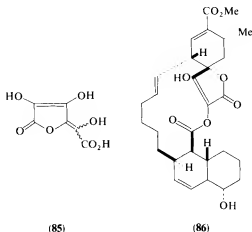
<sup>186</sup> J. F. Grove, *J. Chem. Soc. C*, 2261 (1971).

<sup>187</sup> S. Gelin, *Synthesis*, 291 (1978).

<sup>188</sup> S. Gelin, *J. Org. Chem.*, **44**, 3053 (1979).

<sup>189</sup> P. Bethesti, O. Battesti, and M. Selim, *Bull. Soc. Chim. Fr.*, 2185 (1975).

acid, from its dimeric state to the hydrated monomer.<sup>190</sup> Ascorbic acid forms radical species with ease, and its condensation product with phenylalanine has been shown to be simply tri(2-deoxy-2-ascorbyl)amine, which is oxidized by air to an intensely blue radical.<sup>191</sup> An analog of ascorbic acid can be made by permanganate oxidation of mannaric acid dilactone; it has structure **85** and is completely methylated on oxygen by diazomethane. The product gives a pyrrole derivative with ammonia.<sup>192</sup>



Recognition that the important antibiotic, chlorothricin, contains a 2-hydroxytetronic acid residue in its macrocyclic ring has spurred interest in the area. The pertinent half of the antibiotic structure is represented in diagram **86**, but the tetronic acid part is completely destroyed by basic hydrolysis.<sup>193</sup> Ireland and Thompson have examined synthetic routes to the spirotetronic acid residue and evolved the route sketched in Scheme 48.<sup>194</sup> The next steps involve selective deprotection of the hydroxyl groups and selective reduction of the ester in the presence of the lactonic carbonyl group. Boron bromide was found to demethylate only the  $\alpha$ -methoxyl group, whereas lithium propanthioide (in HMPA) demethylated only the  $\beta$ -methoxyl group; no doubt the former depends upon coordination of boron with carbonyl oxygen, whereas the latter depends upon the superior ability of the  $\beta$ -oxygen to act as a leaving group. Deprotection of both

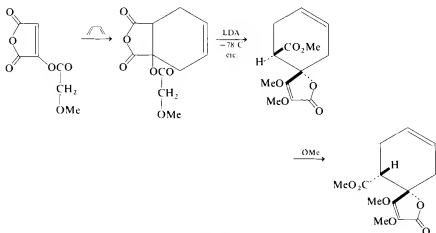
<sup>190</sup> S. Berger, *Tetrahedron* **33**, 1587 (1977).

<sup>191</sup> T. Hayashi and M. Namiki, *Tetrahedron Lett.*, 4467 (1979).

<sup>192</sup> K. Keyns and A. Linkus, *Chem. Ber.* **108**, 3637 (1975).

<sup>193</sup> A. Gerhard, R. Muntwyler, and W. Keller-Schierlein, *Helv. Chim. Acta* **58**, 1323 (1975).

<sup>194</sup> R. E. Ireland and W. J. Thompson, *J. Org. Chem.* **44**, 3041 (1979).



SCHEME 48

hydroxyl groups could not be effected directly, but was satisfactorily accomplished in stages. Direct reduction of the ester to an aldehyde in the usual manner with DIBAL failed because of concomitant reduction of the lactone, but selective reduction to the alcohol by either lithium borohydride or lithium triethylborohydride was possible. After oxidation to the aldehyde a new problem arose concerning selective reaction with organometallic reagents, and here vinylmanganese iodide was found to be superior to the usual magnesium reagent.<sup>194</sup>

In addition to the lactone (77), the bog asphodel (*Narthecium ossifragum* Hud.) contains a racemate assigned structure 87,<sup>177</sup> although the spectroscopic findings were later revised.<sup>195</sup> The plant also produces glucosides, nartheside A being hydrolyzed to the (S)- and nartheside B to the (R)-enantiomer.<sup>195a</sup> These lactones are active against *Bacillus subtilis*<sup>177</sup> and can be prepared from the methyl ether ("ester") of tetric acid by brominating the methylene group and hydrolyzing the product.<sup>195</sup> Irradiation of methyl diazomalonate in molten 1,4-dichlorobenzene leads to a compound shown by X-ray diffraction to have a structure (88) that is essentially dimeric and that is produced, it is thought, because both carbene formation and methoxyketene formation (i.e., the Wolff transformation) occur simultaneously with two species trapping each other across the junction at the wavy line.<sup>196</sup>

<sup>195</sup> T. Reffstrup and P. M. Boll, *Phytochemistry* **18**, 325 (1977).

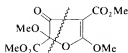
<sup>195a</sup> K. E. Schulte, J. Beisch, and A. Mock, *Arch. Pharm. (Weinheim, Ger.)* **295**, 62 (1962).

<sup>196</sup> K. Eichorn, R. Hoge, G. Maas, and M. Regitz, *Chem. Ber.* **110**, 3272 (1977).

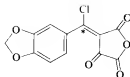




(87)

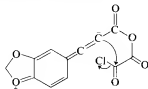


(88)

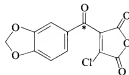


(89)

Finally, the "quinone" offers amusement. Arylpropynoic acids react normally with oxalyl chloride to give acid chlorides unless they bear strongly electron-releasing groups, in which case Crombie *et al.* find that red chloroanhydrides of type **89** are produced, perhaps via the displacement indicated in **90**. According to crystallographic studies, both geometric isomers are present in the crystal. The compound is readily hydrolyzed by water, but a controlled amount affords enols corresponding to **89** (OH for Cl). The chief surprise stems from the rearrangement above 155 °C to the maleic anhydride derivative (**91**); there is no change of position on the benzene ring, and the <sup>14</sup>C label (shown as \*) remains attached to the benzene ring. The authors suggest an oxet intermediate.<sup>197</sup>



(90)



(91)

### E. FURANTHIOLS

Older methods of preparing furanthiols and their derivatives have been overshadowed by lithiation techniques in which the metallated furan is treated with sulfur and alkylated to give the desired alkylthiofurans.<sup>198,199</sup> Phosphoryl thioesters are obtained in the same way, as are their selenium equivalents.<sup>200</sup> 2-Furyllithium affords lithium furan-2-selenite when treated with selenium dioxide.<sup>201</sup>

<sup>197</sup> L. Crombie, R. G. Havard, and D. P. Reynolds, *J. C. S. Chem. Commun.*, 265 (1973); L. Crombie and D. P. Reynolds, *ibid.*, 265.

<sup>198</sup> E. Niwa, H. Aoki, H. Tanaka, K. Munakata, and M. Namiki, *Chem. Ber.* **99**, 3215 (1966).

<sup>199</sup> B. Cederlund, R. E. Lanz, A.-B. Hörnfeldt, O. Thörstad, and K. Undheim, *Acta Chem. Scand., Ser. B* **B31**, 198 (1977).

<sup>200</sup> S. Andreae and H. Seeboth, *Z. Chem.* **19**, 143 (1979).

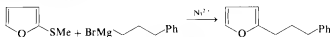
<sup>201</sup> R. Kada, V. Knoppova, and J. Kovac, *Collect. Czech. Chem. Commun.* **43**, 160 (1978).

A new alternative has also been described. The furan is oxidatively methoxylated, and the product condensed with an alkyl or arylthiol by means of an acid catalyst in acetonitrile at ordinary temperatures; it is presumed that a carbocation is intermediate. Although the method makes available aryl thioesters as well as alkyl thioethers, heterocyclic thiols and thiourea fail. The furylthioethers are not very stable and decompose if the reaction is prolonged.<sup>202</sup>

The thiols themselves are best made by the lithiation-sulfur method, followed by acidification.<sup>198,199</sup> IR and NMR studies show that furan-2-thiols and furan-3-thiols are tautomeric but that the thiol, not the thione, is always by far the major isomer. This differs from the oxygen analogs. Evidence from the ionization potentials supports the thiol structure. Furylthioethers have IP values about 0.3 eV higher than do the parent thiols, just as in the benzene series.<sup>199</sup>

Hydrolysis of the 2-thioethers is easily accomplished by acid treatment, but the ring collapses and the product is a mixture of the dialdehydes corresponding to maleic and fumaric acids.<sup>202</sup> Heating 2-furyl allyl thioethers at only 70°C induces a thio-Claisen rearrangement to the 3-position as expected<sup>203</sup>; the reaction is first order with an activation energy of 96 kJ/mol.

A reaction without an oxygen parallel takes place when 2-furyl methyl thioether is treated with a Grignard reagent in the presence of a complex formed from nickel(II) chloride and a 1,3-propadiylbisphosphine derivative (Scheme 49). The sulfur is lost and the Grignard radical takes its place in reasonable yield (59%).<sup>204</sup>



SCHEME 49

Some other facets of furanthiol chemistry have already been summarized in Schemes 26 and 49 (Vol. 30) and 33. 3-Alkylthiofurans are important flavoring agents and form the basis of a series of patents.<sup>205</sup>

## F. FURANAMINES

Furanamines have not been extensively studied. Products of reactions taking unexpected courses are often ascribed furanamine structures without

<sup>202</sup> R. A. Silverman and D. M. Burness, *J. Org. Chem.* **33**, 1869 (1968).

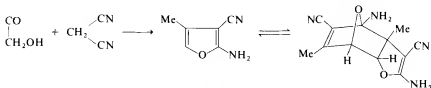
<sup>203</sup> A. V. Anisimov, V. F. Ivanova, and E. A. Viktorova, *Zh. Org. Khim.* **15**, 1970 (1979).

<sup>204</sup> H. Takei, M. Miura, H. Sugimura, and H. Okamura, *Chem. Lett.*, 1447 (1979).

<sup>205</sup> W. J. Evers, H. H. Heinsohn, B. J. Mayers, and E. A. Karoll, U.S. Patent 3,961,093.

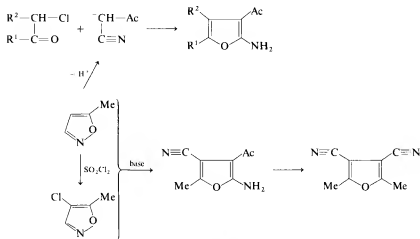
much evidence; such cases are not included here although, of course, some could well be genuine. Limited reviews are available.<sup>206</sup>

Even "obvious" furanamine chemistry provides pitfalls. Isidor *et al.*<sup>207</sup> have shown that whereas the condensation of malononitrile with  $\alpha$ -ketols does give furanamines as claimed in 1966, the lightly substituted furan shown in Scheme 50 is actually not isolated because it dimerizes readily in



SCHEME 50

the [4 + 2] mode giving what is thought to be the first example of a 4,7-epoxybenzofuran (as opposed to a 4,7-epoxyisobenzofuran, examples of which are numerous). Dissociation of the dimer is easy, so that hydrolysis or reaction with furan-2,5-dione still afford products derived from the mononuclear furan. The latter reaction can also supply aniline derivatives. If the expected furanamine is more heavily substituted it does not readily dimerize and can be isolated.<sup>207</sup>



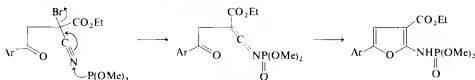
SCHEME 51

<sup>206</sup> M. V. Noritsina and I. N. Klochkova, *Collect. Lect.-Int. Symp. Furan Chem.*, 3rd, 1979, 228 (1979); A. P. Kriven'ko and T. G. Nikolaeva, *ibid.*, 190; R. Kada, V. Knoppova, and J. Kovac, *ibid.*, 186.

<sup>207</sup> J. L. Isidor, M. S. Brookhart, and R. L. McKee, *J. Org. Chem.* **38**, 612 (1973).

Other syntheses utilize cyanide groups both to activate the system and supply amine nitrogen. The sodium enolate of 3-oxobutanonitrile is unstable but easily obtained from the action of base upon 5-methylisoxazole; in a modification of Feist-Benary synthesis it reacts with  $\alpha$ -chloroketones, with the products cyclizing to 3-acetylfuranamines (Scheme 51). As in most authentic furanamines, the existence of a true furan nucleus is sustained by delocalization energy between the amino group and an electron-withdrawing group, here the acetyl substituent. What is special about these acetylfuranamines is the exceptionally intense color they develop with iron salts. They can be conveniently obtained colorless only by sublimation.<sup>208</sup> An ingenious modification of the synthesis takes advantage of the specific chlorination of 5-methylisoxazole by sulfonyl chloride. The product, 4-chloro-5-methylisoxazole, is an equivalent of a chloroketone and the condensation converts it to an aminofurancarbonitrile (Scheme 51), the structure of which could not be securely established by spectroscopic means because these fail to eliminate a possible carboxamide group. The structure was confirmed by X-ray diffraction. Because the nitrile bears two electron-withdrawing groups the ring opens in hot aqueous ammonia and recloses to give 2,5-dimethylpyrrole-4,5-dicarbonitrile. The ester corresponding to the aminonitrile was also made and found to be sensitive to ring opening in alkali.<sup>208</sup>

Leblanc *et al.* have devised an ingenious approach to furanamine synthesis that depends upon a novel use of the  $\alpha$ -bromonitrile grouping (Scheme 52). Nucleophilic attack by triethyl phosphate(III) occurs at the nitrogen atom and ejects the halogen, leaving a ketimine grouping. Enolization and ring closure lead to the phosphoramidate shown.<sup>209</sup>



SCHEME 52

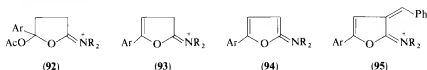
4-Oxoalkanamides can be regarded as 1,4-diketones but application of the Paal-Knorr cyclization is successful only if it yields dialkylaminofurans bearing a 5-aryl substituent. Within these limits, however, the reaction is very useful.<sup>210</sup> The cyclization is effected with acetic anhydride containing perchloric acid, and the initial product (92) contains added acetic acid. Water regenerates the starting dialkylamide or a 4-arylbutenolide; on the

<sup>208</sup> J. F. Blount, D. L. Coffen, and D. A. Katonak, *J. Org. Chem.*, **43**, 3821 (1978).

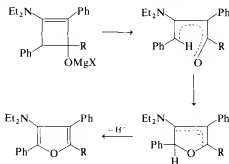
<sup>209</sup> R. Leblanc, E. Corre, M. Soenen-Srlarich, and M. F. Chasle, *Tetrahedron* **28**, 4431 (1972).

<sup>210</sup> G. V. Boyd and K. Heatherington, *J. C. S. Perkin I*, 2523 (1973).

steam bath only the acetic acid is eliminated leaving the salt (93). From this, triethylamine removes a proton to form the desired furanamine (94). Such compounds can be hydrolyzed by acid, but whereas they are stable to bases they are too sensitive to most electrophilic reagents for synthetic elaboration. They couple with diazonium salts and condense with aromatic aldehydes in acid to give 3-arylidene derivatives (95) that can be hydrolyzed to 2-arylidenebutenolides and dialkylamine. They do not add diphenylnitrilimine or aryl azides, but they do add furan-2,5-dione and similar dienophiles in the conventional way, and the products can again be used as a source of benzenoid compounds.<sup>210</sup>



A French group finds that Grignard reagents, which normally replace the amine function in ketoenamines, add to the carbonyl group if the system is part of a cyclobutane ring, as in Scheme 53.<sup>211</sup> Ring opening and reclosure produce the furan nucleus, but there is also a need for removal of hydride ion. There are few other good methods of making 3-aminofuran derivatives.



SCHEME 53

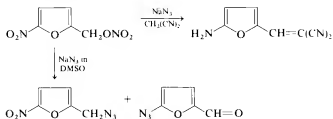
Advances in the preparation of furanamines by nucleophilic substitution are almost entirely lacking. The reaction between aniline and 5-halogenated furfuraldehyde does yield a furanamine derivative (Section III.C, Vol. 30).<sup>211a</sup> In contrast, Lewis and Mulquiney<sup>212</sup> report that aniline converts furfuraldehyde to a cyclopentenone derivative, no fewer than 10 incorrect structures having been suggested previously. One new sequence comes from

<sup>211</sup> J. Ficini, M. Claeys, and J. C. Depezay, *Tetrahedron Lett.*, 3353 (1973).

<sup>211a</sup> E. Niwa, *Chem. Ber.* **103**, 2992 (1970).

<sup>212</sup> K. G. Lewis and C. E. Mulquiney, *Aust. J. Chem.* **23**, 2315 (1970).

Czech laboratories; the nitro nitrate starting material is condensed with malononitrile (which replaces the nitrate group) and sodium azide (which replaces the nuclear nitro group). The main features are displayed in Scheme 54, but the several oxidation-reduction steps implied at various points are not yet clearly understood.<sup>213</sup>



SCHEME 54

The 3-morpholinofuran (**96**), already well known, has received renewed attention from Lutz *et al.*<sup>214</sup> With bromine it forms an immonium salt (**97**) in which the methylenes are nonequivalent because rotation is now difficult. Phenylmagnesium bromide converts this salt partly into the original furan but, because of reaction at the immonium groups, partly into a dibenzoyl-alkene. The bromine atom can be replaced by hydroxyl or alkoxy groups very easily and the compound is a mild brominating agent able to halogenate acetone. A similar salt (**97**; H for Br) is produced merely by dissolving the furan in trifluoroacetic acid.<sup>214</sup>

As in the furanol series, there is a problem of tautomerism with furanamines. In general, aminofurans can exist to some extent as imines; acid hydrolysis frequently eliminates ammonia. Meinwald and his colleagues have studied such 2-aminofuran hydrolyses and found them to give not the expected butenolides but dimers.<sup>215</sup>

Some aminobutenolides have been examined<sup>215a</sup>; none appeared to be enolic. Capuano and Fischer synthesised an enamino-furanone and found that it was not enolic.<sup>216</sup> The spiran (**98**) is particularly interesting, but a recent resynthesis included no study of the problem.<sup>217</sup> A very simple mycotoxin from tall fescue (*Testucca arundinacea* Schreb.) has structure

<sup>213</sup> F. Povazancec, J. Kovac, and D. Heseck, *Collect. Czech. Chem. Commun.* **44**, 3301 (1979).

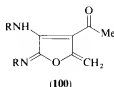
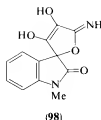
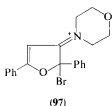
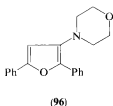
<sup>214</sup> R. E. Lutz, W. M. Harbins, M. G. Hankins, W. J. Welstead, and C. L. Dickenson, *J. Heterocycl. Chem.* **7**, 569 (1970).

<sup>215</sup> G. M. Klein, J. P. Heotis, and J. Meinwald, *J. Org. Chem.* **33**, 1105 (1968).

<sup>215a</sup> J. Baumrucker, M. Calzadilla, T. Rodulfo, and J. Archila, *J. Org. Chem.* **33**, 3991 (1968); W. Steglich, V. Austel, and H. Tanner, *Chem. Ber.* **101**, 916 (1968).

<sup>216</sup> L. Capuano and W. Fischer, *Chem. Ber.* **109**, 212 (1976).

<sup>217</sup> R. G. Amiet, F. W. Eastwood, and J. D. Rae, *Aust. J. Chem.* **25**, 1473 (1972).



**99** and was synthesised by condensing acetamide with 5-bromofuran-2(5*H*)-one; hydrolysis readily gives butandioic acid and (*Z*)-4-oxobut-2-enoic acid.<sup>218</sup>

The only quinoneimine (**100**) to come to notice was obtained by condensing pentan-2,4-dione with the complex formed between mercury(II) chloride and the isonitriles RNC in the presence of triethylamine. Various tautomers are again possible, but that shown is thought to be the chief one.<sup>219</sup>

## IV. Rearrangements and Eliminations

These two aspects of furan chemistry are placed together since neither is particularly extensive and since they often have points in common, especially in reactions leading to methylene dihydrofurans, these being regarded as tautomers of alkylfurans which often rearrange to true furans. Some methylene furans have already been seen as intermediates in various furan syntheses and reactions.

### A. REARRANGEMENTS

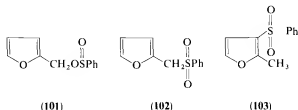
#### 1. Side-Chain Reactions

Side chain reactions considered here are confined to those in which the furan ring plays a clear part. Usually, this is to promote ionic reactions by

<sup>218</sup> E. P. White, *J. Chem. Soc. C*, 346 (1967); H. J. Burkhardt, R. E. Lundin, and W. H. McFadden, *Tetrahedron* **24**, 1225 (1968).

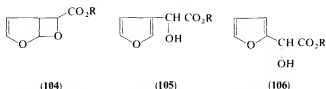
<sup>219</sup> H. Sawai and T. Talcizawa, *Chem. Pharm. Bull.* **23**, 2842 (1975).

way of electron release as in the equilibrium between furfuryl thiocyanate and isothiocyanate where the rates are first order in most solvents and where the equilibrium is little affected by temperature.<sup>220</sup> A more complex situation arises if the furfuryl cation acts as a bidentate ligand. When the sulfinate (101) rearranges in a hydroxylic solvent it suffers both solvolysis and a rearrangement to the furfuryl sulfone (102), but when it rearranges in a nonsolvolytic solvent it gives two sulfones, the second (103) resulting from



attack at position 3 of the furan ring. Both rearrangements are prevented by strongly electron-withdrawing substituents (5-nitro) or promoted by electron donors (an  $\alpha$ -methyl group produces spontaneous rearrangement at  $-70^\circ\text{C}$ ), and the isomer ratio is strongly affected by solvent polarity (nonpolar solvents favor the 3-sulfone). All kinetics are unimolecular. Concerted sigmatropic allylic rearrangements of sulfinates to sulfones are known but it is thought that both kinds of furan rearrangement are ionic, possibly involving specific ion pairs.<sup>221</sup>

A somewhat similar problem is revealed by the acid-catalyzed ring opening of oxetans (104). These are formed by photochemical  $[2 + 2]$  additions, and with boron fluoride or aluminium chloride they supply 3-furylecarbinols (105) mixed, however, with the isomeric 2-furylecarbinols (106). With toluene-sulfonic acid only the expected 3-furylecarbinol results, but this is changed into the 2-isomer when treated with one of the Lewis acids. The rearrangement is believed to be effected by dissociation into furan and a carbenium ion  $\text{XOCHCO}_2\text{R}$ : in support, added methylfuran will trap some of this ion, and if the migrating center is optically active, the products are racemic.<sup>222</sup>



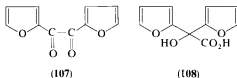
<sup>220</sup> L. A. Spurlock and R. G. Fayer, *J. Org. Chem.* **34**, 4035 (1969).

<sup>221</sup> S. Braverman and T. Globberman, *Tetrahedron Lett.*, 3023 (1973); *Tetrahedron* **30**, 3873 (1974).

<sup>222</sup> S. Jarosz and A. Zamejski, *J. Org. Chem.* **44**, 3720 (1979).

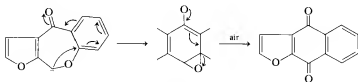


In the benzil analog (107) a benzilic acid rearrangement leading to the acid (108) can be done and the acid isolated either as a salt or as the methyl ester prepared with diazomethane at a low temperature. The surprise lies in the fact that the acid (108) is unexpectedly unstable in the free state; what



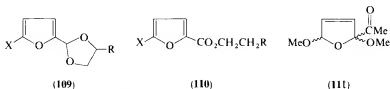
has passed for many years as methyl furilate is actually only methyl 2-furoate. True furilic acid is itself acid sensitive and even in acetic acid it undergoes the well-known general reaction in which an  $\alpha$ -hydroxy-acid loses CO and H<sub>2</sub>O to give a ketone (here the 2,2'-difuryl ketone).<sup>223</sup>

A quite different base-catalyzed reaction was discovered by French workers in their studies of 2,3-disubstituted furans and pyrroles.<sup>224</sup> They prepared a furooxepinone by standard methods and treated it with hot potassium ethoxide in ethanol to obtain a furoquinone. Scheme 55 shows one way in which this result can be rationalized; the salient feature is that the benzene, and not the furan ring is disrupted, despite the large discrepancy in delocalization energies (150 vs 80 kJ mol<sup>-1</sup>).



SCHEME 55

Russian workers report a thermal rearrangement in the side chain of furfurylidene acetals (109). The products are esters (110) and are formed in high yield (>90%).<sup>225</sup> One can expect the influence of all three oxygen



<sup>223</sup> S. Pennanen, *Acta Chem. Scand.* **26**, 1280 (1972).

<sup>224</sup> C. Rivalle, E. Bisagni, and J. Andre-Louisfert, *Tetrahedron* **30**, 3193 (1974).

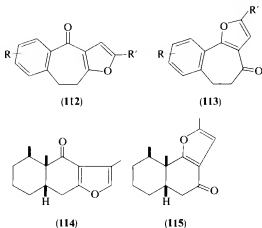
<sup>225</sup> V. G. Kul'nevich, Z. I. Zelikman and S. E. Tkachenko, *Khim. Geterotsikl. Soedin.*, 1327 (1976); Z. I. Zelikman, *Tr. Krasnodar. Pol'tekh. Inst.* **66**, 41 (1975).

stems to combine in promoting what at some stage must require a hydride transfer.

Beckmann rearrangements applied to 2-furyl ketones are abortive; there is no skeletal rearrangement. Many studies have failed to elucidate exactly what happens, but recently it has been demonstrated by methods including alternative synthesis that the products from oxime tosylates in methanol are actually 2,5-dimethoxy-2,5-dihydrofurans (e.g., **111** from 2-acetylfuran) as mixtures of geometrical isomers exactly as if they had been formed by furan oxidation techniques (Section VI; Part I).<sup>226</sup>

## 2. Ring Reactions

New examples of known rearrangements of 3-acylfurans have been described in which the ring opens and reforms on the acyl oxygen atom. The isomerization of **112** to **113** is effected by protic or Lewis acids,<sup>227</sup> whereas the change from ligularone (**114**) to isoligularone (**115**), which occurs



at 260°C without a catalyst, is interpreted by means of biradical intermediates.<sup>228</sup> New examples of the Marckwald reaction,<sup>229</sup> together with some other evidence suggests that in some cases the acyclic diketoacid is a true intermediate (Scheme 56).<sup>230</sup> All the main features can be convincingly

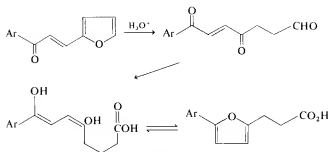
<sup>226</sup> B. B. Greene and K. G. Lewis, *Aust. J. Chem.* **21**, 1845 (1968); A. F. Oleinik, *Khim. Geterotsikl. Soedin.*, 1026 (1975).

<sup>227</sup> C. Rivalle, J. André-Louisfert, and E. Bisagni, *Tetrahedron* **32**, 829 (1976).

<sup>228</sup> M. Tada and T. Takahashi, *Tetrahedron Lett.*, 3999 (1973).

<sup>229</sup> F. D. Popp, W. R. Schleigh, and L. E. Katz, *J. Chem. Soc. C*, 2253 (1968); M. M. Coombs and S. B. Jaitly, *ibid.*, 230 (1971).

<sup>230</sup> F. W. Short and G. M. Rockwood, *J. Heterocycl. Chem.* **6**, 713 (1969).



SCHEME 56

explained except the oxidation–reduction step. The acid-catalyzed rearrangement of 2-furylcarbinols to cyclopentenones (Scheme 31, Part I) has synthetic value; a similar rearrangement now seems likely to underlie the puzzling reaction between furfuraldehyde and aniline.<sup>212</sup>

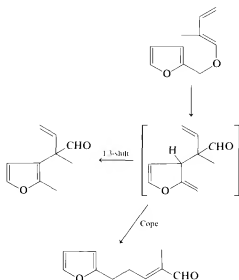
### 3. Claisen, Cope, and Hetero-Cope Rearrangements

Under carefully specified conditions the vacuum pyrolysis of 2-(1,3-butadienyl)furan smoothly provides 4,5-dihydrobenzofuran by way of a nonaromatic intermediate and a 1,5-sigmatropic suprafacial hydrogen shift. As a check, deuterium at the terminal methylene group of the butadiene chain was shown to reside at position 4 in the product.<sup>231</sup>

Simple vinyl ethers can be rearranged only with difficulty; several products being formed all of which can be understood as originating from radical pairs.<sup>232</sup> Rearrangement is easier and much more specific if another double bond can assist it. The requisite ethers are readily prepared from furan-methanol and a vinyl ether in the presence of mercury(II) chloride; at 100°C and above they commence to rearrange (Scheme 57). The initial product has two options: it can simply transpose hydrogen giving a 3-substituted 2-methylfuran or it can undergo a Cope rearrangement leading to a furan carrying one long side chain at the 2-position. The second option is preferred and allows syntheses of several naturally occurring furans including perillene, dendrolasin, and (by a double homologation) the aldehyde (**116**) named torreyal because it was isolated from the oil of *Torreya nucifera* Sibe. & Zucc. Similar rearrangements of 3-furanmethanol derivatives are possible although somewhat less easily so.<sup>232</sup>

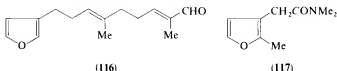
<sup>231</sup> B. J. Rosen and W. P. Weber, *Tetrahedron Lett.*, 151 (1977).

<sup>232</sup> A. F. Thomas, *Helv. Chim. Acta* **53**, 605 (1970); *Chem. Commun.*, 1657 (1968); A. F. Thomas and M. Ozainne, *J. Chem. Soc. C*, 220 (1971).



SCHEME 57

The same theme runs through several other methods for making 2,3-disubstituted furans. 2-Furanmethanol is easily transformed into the amide (117) by Eschenmoser's method, i.e., heating with the methoxyenamine



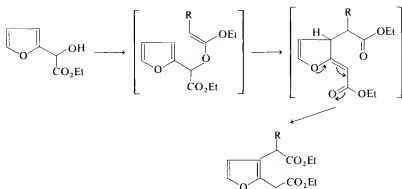
$\text{CH}_2=\text{C}(\text{OMe})\text{NMe}_2$  in DMF for 24 hr at 160 C.<sup>233</sup> Hydroxyesters can be made from furfural cyanohydrin and when heated with an orthoester afford vinyl ethers that rearrange in a similar manner (Scheme 58).<sup>234</sup> The ester substituent appears to promote the rearrangement by stabilizing the intermediate.

In sesquiterpenoids of the germacrane type a furan ring is often a structural feature that can have a subtle influence on the stereochemistry of Cope rearrangements within the large ring even though its own double bonds are not implicated.<sup>235</sup> Thus, the *E,Z*-double bond geometry in 118 should

<sup>233</sup> Ta-jyh, *Tetrahedron Lett.*, 2297 (1979).

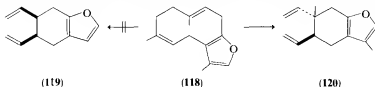
<sup>234</sup> S. Raucher, A. S.-T. Lui, and J. E. Macdonald, *J. Org. Chem.* **44**, 1885 (1979).

<sup>235</sup> K. Takeda, I. Horibe, and H. Minato, *J. Chem. Soc. C*, 2704 (1970); *J. C. S. Perkin I*, 2212 (1973); H. Hikino, C. Konno, K. Agatsuma, T. Takemoto, I. Horibe, K. Tori, M. Ueyama, and K. Takeda, *ibid.*, 478 (1975).



SCHEME 58

direct the Cope rearrangement into the *cis*-divinyl product (**119**), whereas actually only the *trans*-divinyl product (**120**) is found. Such abnormal



rearrangements require a temperature rather higher than usual (between 200 and 300° C) and consequently it is thought that in a 10-membered ring already containing both an (*E*)- and a (*Z*)-double bond the additional constraint resulting from a stiff furan double bond is enough to upset the usual rules (e.g., the operation of a chair-shape transition state). Takeda, who has made major contributions to these studies, has reviewed them.<sup>236</sup>

#### 4. Prototropy

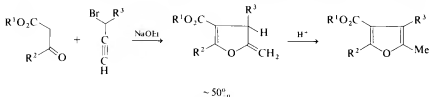
In theory, a prototropic shift in 2-methylfuran should be difficult because the product, 2-methylene-2,3-dihydrofuran, must lack aromaticity. And indeed no shift of this kind is known. Recently, it has become clear that the converse is not true; 2-methylene-2,3-dihydrofurans do not easily revert to aromatic furans, as was once commonly assumed, but are often stable. They have become the subjects of legitimate study. Indeed, there are even some natural products in this class.

Nevertheless, the stability of methylenedihydrofurans is kinetic in origin and isomerization is usually easy.<sup>237</sup> Generally, such compounds are stable

<sup>236</sup> K. Takeda, *Tetrahedron* **30**, 1525 (1974).

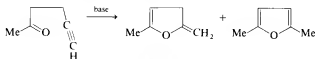
<sup>237</sup> S. Divald, M. C. Chun, and M. M. Joullie, *Tetrahedron Lett.*, 777 (1970).

in neutral or basic media, and since they are vinyl ethers they are very unstable in acid. Scheme 59, part of a furan synthesis due to Couffignal,



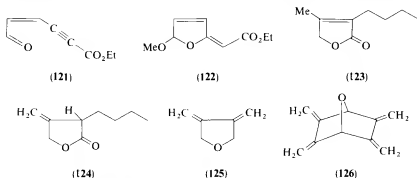
SCHEME 59

illustrates this point.<sup>238</sup> The internal addition of alkoxide to alkyne would appear to be a reliable route to methylenedihydrofurans even under relatively vigorous conditions. Scheme 60 provides an example described by Doutheau



SCHEME 60

and Goré<sup>2,38a</sup> who also offer a general discussion of this cyclization. Several other examples are contained within references quoted in Part I, Sections II, F and G. A useful variant begins with a diazomethylfuran derivative from which, as noted already (Section V, B, Part I), acetylenic aldehydes (**121**) are formed by elimination of nitrogen. With such aldehydes, silver ion in methanol provides a very satisfactory route to exomethylenefuran derivatives (**122**).<sup>2,39</sup> Despite the activating ester substituent, prototropy aromatizing the system is apparently unimportant or slow; the same phenomenon is characteristic of the reactions of chloromethylfurans with cyanide ion



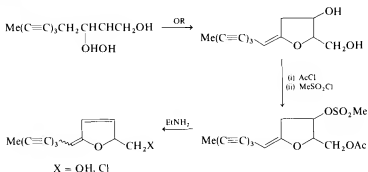
<sup>238</sup> R. Couffignal, *Synthesis*, 581 (1978)

<sup>238a</sup> A. Doutheau and J. Goré, *Tetrahedron* **32**, 2705 (1976).

<sup>239</sup> R. V. Hoffman and H. Schechter, *J. Org. Chem.* **39**, 2939 (1974).

(Section III.C, Part I), the methylenefuran intermediates being fairly stable in moderate base and easily isolated.<sup>239a</sup>

Bohlmann and Weber have discovered in certain members of the Inuleae a number of halogen compounds including an exomethylene furan. Scheme 61 shows the main points of their synthesis of this compound, which seems not to undergo any easy isomerization.<sup>240</sup> Yet more surprising is the report that the fungus, *Hypoxylon serpens*, contains in addition to the butenolide (123) its exomethylene tautomer (124), believed to be the first example of such a compound as a natural product. Since the lactone group activates it, the proton does spontaneously move to produce the ordinarily butenolide (123), but even so the process takes several months in the absence of catalysis.<sup>241</sup>



SCHEME 61

Doubly prototropic furans are known. The simplest (125) is unstable but can be obtained in 15% yield by treating tetra(bromomethyl)ethene with sodium hydroxide. The product lacks an IR band at  $1725\text{ cm}^{-1}$  that had been noted in a different preparation, now thought to indicate contamination by acetic acid.<sup>242</sup> Another such compound has structure 126, remarkable because the butadiene chromophores react strongly across the ring.<sup>243</sup> No special sensitivity is reported, and aromatization would of course be prevented because of the inordinate strain imposed according to Bredt's rule. The plant *Lindera obtusiloba* Blume elaborates as a main component of its leaves a furan derivative known as obtusilactone<sup>244</sup>; structure 127 possesses

<sup>239a</sup> S. Divald, M. C. Chun, and M. M. Joullié, *Tetrahedron Lett.*, 777 (1970); *J. Org. Chem.* **41**, 2835 (1976).

<sup>240</sup> F. Bohlmann and R. Weber, *Chem. Ber.* **105**, 3036 (1972).

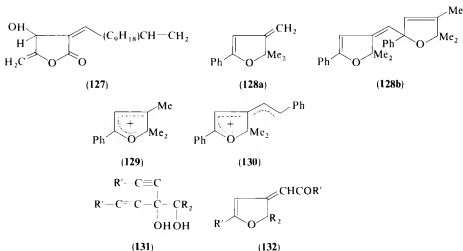
<sup>241</sup> R. L. Edwards and A. J. S. Whalley, *J. C. S. Perkin I*, 803 (1979).

<sup>242</sup> Y. Gaoni, *Tetrahedron Lett.*, 2361 (1973).

<sup>243</sup> P. Vogel and A. Florey, *Helv. Chim. Acta* **57**, 200 (1974).

<sup>244</sup> M. Niwa, M. Iguchi, and S. Yamamura, *Tetrahedron Lett.*, 1539 (1975).

a most unusual arrangement tantamount to an exomethylene form of a tetrone acid (Section III,C). We mention another exomethylene furan (**128a**) because it may shed light on "instability" of furan tautomers other than their tendency to aromatize. Prepared from the appropriate 3-furanone by treatment with methyllithium, this compound in trichloromethane dimerizes in less than a day to a product tentatively assigned structure **128b**.<sup>245</sup> In acid media, on the other hand, it exists as the dihydrofurylium salt (**129**), which is more stable and which is obtained directly by treating the acetylenic diol  $\text{PhC}\equiv\text{CC}(\text{OH})(\text{Me})\text{C}(\text{OH})\text{Me}_2$  with perchloric acid.<sup>246</sup> Such salts are also discussed in Section III,B (Vol. 30); they contain "active methyl" and will condense with aromatic aldehydes to give styrylfurylium salts (**130**).<sup>246</sup> Treatment of the diacetylenic diol (**131**) with a mercury salt in acidic methanol precipitates the yellow acylmethylene derivatives (**132**).<sup>247</sup>



## B. ELIMINATIONS

Pyrolysis of the ammonium salt (**133**) at 150 C as a preparative method for 2,5-dimethylenefuran (**134**) was introduced by Wynberg *et al.*<sup>248</sup> in 1960. It has been extensively used in one form or another for the preparation of

<sup>245</sup> P. S. Mariano and M. Peters, *Tetrahedron Lett.*, 2607 (1974).

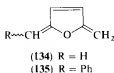
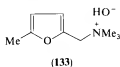
<sup>246</sup> A. Fabryey, *Zh. Obshch. Khim.* **31**, 1548 (1961); *Chimia* **15**, 552 (1961); *Rocz. Chem.* **40**, 1657 (1966).

<sup>247</sup> A. Fabryey and Z. Wichert, *Tetrahedron Lett.*, 1307 (1977).

<sup>248</sup> H. E. Wynberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.* **82**, 1428 (1960).

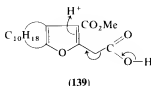
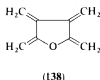


furan cyclophanes described below in Section V, B. Elimination can be so easy as to constitute a nuisance, as in cases described in Sections V.A and C. A more recent variation conveniently provides the phenyl derivative (135) as an orange solid.<sup>249</sup> The retro-Diels-Alder reaction in 136 has been used



to provide the isomeric 2,3-dimethylenefuran (137) as a colorless material that polymerized very readily but could be trapped by various addenda in cycloaddition reactions.<sup>250</sup> Such eliminations are of course common in the mass spectrometry of furans.<sup>251</sup> For the corresponding double elimination from octahydrodibenzofuran affording the heteroradialene tetramethylenefuran (138), the temperature was between 920 and 940°C. The compound was sufficiently stable so that its <sup>1</sup>H- and <sup>13</sup>C-NMR spectra could be determined at -50°C. At -40°C it changed into an insoluble white polymer.<sup>252</sup>

Decarbonylations of furfuraldehyde to furan continue to be of commercial interest and various new catalysts have been recommended.<sup>253</sup> Decarboxylations are still occasionally useful,<sup>254</sup> and the selective decarboxylation of furan-3,4-dicarboxylic acid to furan-3-carboxylic acid is said to be much improved by omitting any solvent.<sup>255</sup> The easy decarboxylation of furan acetic acid derivatives is formulated in structure 139, although the acidic conditions need not preclude ring opening.<sup>255a</sup>



<sup>249</sup> I. Stiber, M. Janda, and J. Srogl, *Collect. Czech Chem. Commun.* **43**, 1481 (1978).

<sup>250</sup> J. Jullien, J. M. Pechine, E. Perez, and J. J. Piade, *Tetrahedron Lett.*, 3079 (1979).

<sup>251</sup> C. W. J. Brooks and G. Draffan, *Tetrahedron* **25**, 2865 (1969).

<sup>252</sup> J. Jullien, J. M. Pechine, E. Perez, and J. J. Piade, *Tetrahedron Lett.*, 611 (1980).

<sup>253</sup> S. Hillers, A. Ya. Karmil'chik, V. Stonkus, B. S. Katayev, and M. V. Shimamskaya, *Prep. Catal., Proc. Int. Symp.*, 1975, 579. (1976); N. Takamiya, K. Korizumi, M. Takano, and S. Murai, *Nippon Kagaku Kaishi*, 1141 (1979).

<sup>254</sup> W. A. Remers and G. S. Jones, *J. Heterocycl. Chem.* **12**, 421 (1975).

<sup>255</sup> L. W. Deady and R. A. Shanks, *Synthesis*, 571 (1972).

<sup>255a</sup> O. Campos and J. M. Cook, *J. Heterocycl. Chem.* **14**, 711 (1977).

## V. Macrocycles

Continuous interest in macrocyclic systems containing furan rings spans more than 25 years. Very often the furan ring has been used merely as a structural element, the interest of the work lying elsewhere; sometimes the macrocyclic system contains heterocyclic units other than furan rings. We shall confine ourselves to macrocycles containing furan units where the chemistry of the furan is more than passing interest. Readers concerned with a much fuller account can consult the review by Newkome *et al.*<sup>256</sup>

### A. QUATERENES AND CROWN ETHERS

The tetraoxaquaterenes are crown ethers of general type **140**; they have been known longer than other macrocyclic systems and do not presently attract much attention. They are easily made by condensing furan with a carbonyl compound in acidic media. As explained in Section III.A (Vol. 30), the condensation is sequential and can often be interrupted at the bis- or tris-furan stages. The condensation product from furan and cyclohexanone is the quaterene (**140a**) and not cyclohexenylfuran as previously thought.<sup>257</sup> The yields in such reactions are often poor because polymerization predominates; Chastrette and Chastrette have improved yields by conducting the condensations in the presence of metallic cations known to complexes with macrocyclic polyethers. That the metallic cation does act as a "template" is suggested by the improved yields (up to 43%) and the inability of tetrabutylammonium salts to produce results comparable to that exerted by Li, Ca, and Mg salts (perchlorates best). Yet the quaterene (**140b**) can form only weak complexes, for none could be isolated; after saturation by hydrogen over nickel, however, the corresponding hydrofuran macrocycle was formed and readily gave a 1:1 complex with  $\text{LiClO}_4$ .<sup>258</sup> Of course the furan oxygen atom can be expected to be rather a weak electron donor to external systems.

Crown ethers of general structure **141** are obtained by allowing 2,5-furanbismethanol (**142a**) to react with polyethylene glycol ditosylates<sup>259,260</sup>; the reverse condensation, in which the dihalide (**142b**) is treated with the dipotassium salt of the glycol, is not viable because the salt, acting as a base,

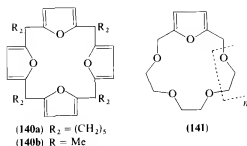
<sup>256</sup> G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.*, **77**, 513 (1977).

<sup>257</sup> W. H. Brown and B. J. Hutchinson, *Can. J. Chem.*, **56**, 617 (1978).

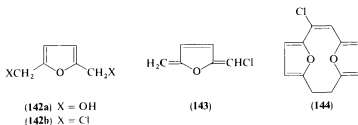
<sup>258</sup> M. Chastrette and F. Chastrette, *J. C. S. Chem. Commun.*, 534 (1973).

<sup>259</sup> J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 4207 (1977).

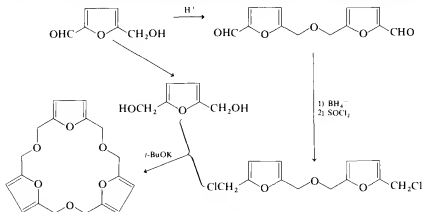
<sup>260</sup> D. N. Reinhardt and R. T. Gray, *Tetrahedron Lett.*, 2105 (1975).



mainly converts the dihalide to the exomethylene furan (143) and so to the cyclophane (144).<sup>259</sup> Cram and his colleagues have also produced a number



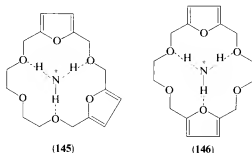
of furan-containing crown ethers by various modifications of a general scheme. The single example (Scheme 62) chosen is one in which the sole



SCHEME 62

organic starting material is sucrose.<sup>259</sup> The same workers confirmed that hydrogenation of the individual furan units is always *cis* on Raney nickel catalysts, but they found no correlation between units so that the macrocycles give mixtures of *syn* and *anti* products. All the saturated systems form more stable complexes with *t*-butylammonium ion (thiocyanate anion) than

the furan parents. Clearly, as predicted, the furan oxygen atom is unable to form strong hydrogen bonds, and the association constants fall by a factor of 12–16 for every ether oxygen in a crown ether replaced by a furan. Again, the constant falls by about 50 in passing from complex **145** to the isomeric complex **146**, the latter employing one furan oxygen atom for binding purposes.<sup>261</sup> Complexation data are critically discussed by Gray and Reinhoudt.<sup>262</sup>



Recently, furan diesters (**147**) have been obtained from 2,5-furandicarbonyl chloride or its 3,4-dimethoxy derivative and the requisite glycol. They have been compared with corresponding benzene and pyridine compounds. All form complexes with metallic cations and with ammonium salts. Those in the furan (**147a**) and benzene series share the property of best forming kinetically stable complexes with benzylammonium cation when there are 24 atoms in the ring; with the pyridine analog the 18-atom ring is best. For complexing the methylammonium cation, however, the 21-atom ring is best. The IR frequencies of the carbonyl group and the UV spectra of the furan unit remain unaltered, showing that this nucleus plays little or no part in the phenomenon; correspondingly, the <sup>1</sup>H-NMR spectra show by shielding effects that the benzyl group must lie over the methylene group furthest from the furan ring, consistent with the relatively weak donor properties of furan oxygen. These donor properties can be increased by electron release from methoxy groups in **147b** and reduced by nitro groups in **147c**.<sup>263</sup>

A related crown ether (**148**) has been made from ethyl 3,4-dihydroxyfuran-2,5-dicarboxylate, bromochloromethane, and base, but it has not been much studied.<sup>264</sup> Crown ethers containing nitrogen atoms are easily obtained from

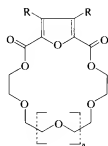
<sup>261</sup> J. M. Tímko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.* **96**, 7097 (1974).

<sup>262</sup> R. T. Gray and D. N. Reinhoudt, *Tetrahedron Lett.*, 2109 (1975).

<sup>263</sup> J. S. Bradshaw, S. L. Baxter, D. C. Scott, J. D. Lamb, R. M. Izatt, and J. J. Christensen, *Tetrahedron Lett.*, 3348 (1979).

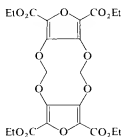
<sup>264</sup> F. Dallacker and V. Mues, *Chem. Ber.* **108**, 569 (1975).

2,5-furandicarbaldehyde (**149**) and polyether diamines.<sup>265</sup> [This dialdehyde was formerly made by oxidation of 5-hydroxymethylfurfural or furan-2,5-bismethanol with  $\text{Pb}(\text{OAc})_4$  and  $\text{MnO}_2$ , but pyridinium chlorochromate has been found to be much better.<sup>266</sup>] Products of type **150** form interesting complexes with metal cations, especially strontium, but again the furan oxygen atom is not implicated.<sup>265</sup> The members of a series of 19 crown ethers containing sulfur and derived from the bisfuran (**151**) have been

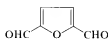


(147a) R = H

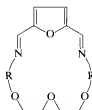
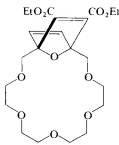
(147b) R = OMe

(147c) R = NO<sub>2</sub>

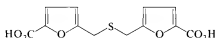
(148)



(149)

(150) R = 1,2-phenylene or  $(-\text{CH}_2)_2$ 

(152)



(151)

<sup>265</sup> D. E. Fenton, D. H. Cook, I. W. Nowell, and P. E. Walker, *J. C. S. Chem. Commun.*, 623 (1977).

<sup>266</sup> T. M. Crespi and F. Soandheimer, *J. Am. Chem. Soc.* **99**, 194 (1977).

prepared by Armenian scientists in yields varying from 11 to 77% but have not as yet been examined for their complexing abilities.<sup>267</sup>

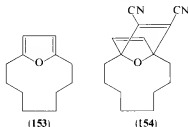
The monofuran crown ethers (**141**) add ethyl butyrdioate in the usual way. One of the products, structure **152**, is interesting because gel permeation separates it into two isomers; NMR studies at 25–163 C establish that interconversion occurs when the large ring or "necklace" passes over the furan oxygen atom but not over the vinyl group. To pass over the vinyl group an energy barrier larger than 84 J/mol must be surmounted. At about 215 C on GLC columns the adduct dissociates into its components.<sup>259</sup>

## B. CYCLOPHANES

### 1. [*n*] (2,5)Furanophanes

The simple [8] (2,5)heterocyclophane (**153**) is thought to be under slight strain because its UV absorption maximum at 225 nm ( $\log \epsilon 3.91$ ) shows a red shift in comparison with that of 2,5-dimethylfuran. However, it is very easily prepared by the Paal-Knorr method ( $P_2O_5$  in ethanol) from cyclo-dodecane-1,4-dione.<sup>268</sup> It readily yields the corresponding pyrrole with ammonia and the thiophene with phosphorus(V) sulfide. At ordinary temperatures the furylic methylene groups appear as simple triplets in the <sup>1</sup>H-NMR spectrum and there is free movement of the chain over the oxygen atom; but two protons always appear at a rather high field near  $\delta$  1.0, and if the temperature falls to –97 C another proton resonates at the yet higher field  $\delta$  0. No doubt the anisotropy of the furan ring is responsible, although the responsible interaction cannot be specified exactly.<sup>268</sup>

Compound **153** readily adds ethynedicarbonitrile; the product (**154**) (cf. **152**) is a "paddlane" and represents a molecule in which carbon (here the



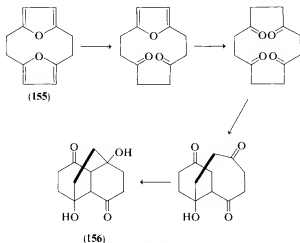
<sup>267</sup> S. A. Vartanyan, T. R. Akopyan, E. G. Paronikyan, and D. A. Avakimyan, *Arm. Khim. Zh.* **32**, 19 (1979).

<sup>268</sup> H. Nozaki, T. Kayama, and T. Mori, *Tetrahedron* **25**, 5357 (1969); J. F. Haley, S. M. Rosenfeld, and P. M. Keehn, *J. Org. Chem.* **42**, 1379 (1977).

bridgehead carbons) might be forced into a planar instead of a tetrahedral configuration.<sup>269</sup> But this is not the case. At  $-100^\circ\text{C}$  the  $^1\text{H-NMR}$  spectrum shows extra splittings that may indicate a special conformation. Models show that, as usual, the methylene necklace can pass freely over the furan oxygen atom but not over the other bridges.<sup>269</sup> The ease with which acid hydrolysis of [8] (2,5)furanophanes takes place facilitates preparation of the corresponding thiophenes and pyrroles by the Paal-Knorr method; strain may facilitate hydrolysis.<sup>268</sup>

## 2. [2.2] (2,5)Furanophanes

Strain effects are larger when there is unsaturation in the bridging ring, so that even aqueous formic acid converts the [2.2] furanophane (**155**) to the bridged naphthalenone (**156**) via polycarbonyl intermediates that recycelize before isolation (Scheme 63).<sup>270</sup> Strain is also likely to be partly responsible



SCHEME 63

for the mass spectral fragmentation pattern of [2.2] cyclophanes (**155**), which consist mainly of fragment ions derived by fission of the central bonds in the ethane bridges.<sup>271</sup> Photolysis of **155** also breaks the ethane bridges in a [6 + 6] cleavage producing 2,5-dimethylene furan which is isolable at  $-78^\circ\text{C}$ .<sup>272</sup> Such reactions regenerate the exomethylene systems from which

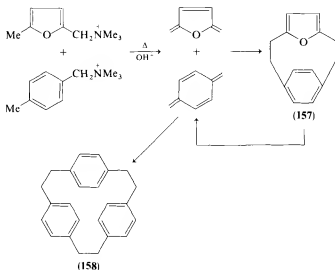
<sup>269</sup> R. Helder and H. Wynberg, *Tetrahedron Lett.*, 4321 (1973).

<sup>270</sup> H.-G. Fritz, H. Henke, and H. Musso, *Chem. Ber.* **107**, 3164 (1974).

<sup>271</sup> H. H. Wasserman and P. M. Keehn, *Tetrahedron Lett.*, 3227 (1969).

<sup>272</sup> G. Jaupp, *Angew. Chem., Int. Ed. Engl.* **15**, 442 (1976).

the cyclophanes were originally obtained. They are still normally made by the method introduced by Wynberg and his colleagues.<sup>248</sup> A 2,5-dimethylenefuran or similar intermediate is generated by elimination (Section IV,B) in the absence of light and air and in the presence of a radical inhibitor and allowed to polymerize spontaneously, a major product being the dimer, or cyclophane. Mixed systems are made by the cogeneration of two exomethylene intermediates although, of course, a mixture results and the yields can be very poor. The furanophane (**157**) can be made reasonably well in this manner, but strain gradually changes it into [2.2.2] paracyclophane (**158**) (Scheme 64). Even at ordinary temperatures there must be some dissociation into the parent exomethylene precursors, but the furan was lost in the gum that was also formed.<sup>273</sup>



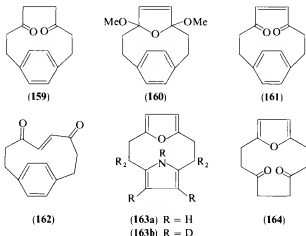
SCHEME 64

Furanophanes afford unsaturated as well as saturated dione bridged compounds. Thus, upon mild acid hydrolysis, **157** gives the dione (**159**), and with bromine in methanol the dihydromethoxyfuran (**160**). With sodium acetate **160** gives (*Z*)-enedione (**161**), but even very gentle treatment with acid induces isomerization to the (*E*)-isomer (**162**).<sup>273</sup> A most interesting, and unexpected, discovery is that [2.2] (2,5)furano(2,5)pyrrolophane (**163a**) suffers selective hydrolysis not at the furan but at the pyrrole ring, giving

<sup>273</sup> D. J. Cram, C. S. Montgomery, and G. R. Knox, *J. Am. Chem. Soc.* **88**, 515 (1966); see also A. C. Cope and B. A. Pawson, *J. Am. Chem. Soc.* **90**, 636 (1968).



the furanophane dione **164** and ammonia.<sup>274</sup> Deuteration and recyclization of the dione with deuterated ammonia supplied the isotopic furanophane (**163b**) with a decoupled <sup>1</sup>H-NMR spectrum simple enough for conformational analysis by variable temperature studies.<sup>275</sup> The NMR spectrum was invariant up to 190 °C, and it was concluded that the aromatic rings cannot rotate within the bridging framework, the minimum Arrhenius activation energy being somewhere near 110 J/sec. Yet in other closely related furanophanes, such as **155**, rotation is fairly free, coalescence being at about -40 °C with  $E_{act}$  near 46 J/mol.<sup>276,277</sup> The imine hydrogen in **163** prevents rotation, but whether this is purely a bulk effect or something owing to hydrogen bonding is not known.



Multilayered cyclophanes have been prepared that show much the same properties regarding strain or rotation of furan units; examples include **165**<sup>278</sup> and **166**.<sup>279</sup> New features emerge from studies of compounds like the [2.2] (1,4)naphthaleno(2,5)-furanophane (**167**) in which rotation of the furan units is possible while there is yet a strongly preferred conformation; in the case of **167** the anti form shown. As a result, the naphthalene proton  $H_b$  suffers rather strong shielding by the furan ring and its resonance moves upfield by about 0.9 ppm, whereas the furan proton  $H_a$  is not much affected.<sup>271</sup> The NMR results have been confirmed by an X-ray diffraction

<sup>274</sup> S. Rosenfeld and P. M. Keehn, *Tetrahedron Lett.*, 402 (1973).

<sup>275</sup> S. M. Rosenfeld and P. M. Keehn, *J. C. S. Chem. Commun.*, 119 (1974).

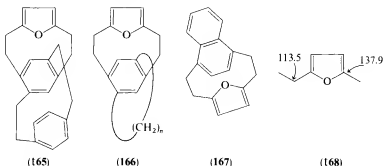
<sup>276</sup> I. Gault, B. J. Price, and I. O. Sutherland, *J. C. S. Chem. Commun.*, 540 (1967).

<sup>277</sup> G. M. Whitesides, B. A. Pauson, and A. C. Copes, *J. Am. Chem. Soc.* **88**, 515 (1966).

<sup>278</sup> N. Osaka, S. Mizogami, T. Otsubo, Y. Sakata, and S. Misumi, *Chem. Lett.*, 515 (1974).

<sup>279</sup> M. Nakazaki, K. Yamamoto, and S. Tanaka, *J. Org. Chem.* **41**, 4081 (1976).

study which shows that the furan ring is planar and inclined to the naphthalene plane at about  $22^\circ$ , while the plane formed by the methylene carbon atoms is inclined at an angle of  $83^\circ$  to that same reference plane, although this is somewhat buckled. The bridging ring is boat shaped, and angles about the furan ring are increased (see structure **168**). The strain inherent in the system is not accommodated in any one bond or angle but is spread among all the structural features, and it accords with intuition that the molecule should attempt to minimize  $\pi$ - $\pi$  repulsion by placing the "small" oxygen atom over the naphthalene ring and setting the furan plane at an angle.<sup>280</sup> There is also good evidence that even in the [2.2] furanophane (**155**) an anti conformation is preferred.<sup>281</sup>



The anthracene analog (**169**), first obtained by Wynberg and Helder,<sup>282</sup> presents a more extreme situation. Shana *et al.* found its  $^1\text{H-NMR}$  spectrum to be invariant with temperature over a wide range, an observation requiring either that rotation is entirely free or that there is no rotation at all. The former hypothesis being untenable, the latter is accepted, and the furan ring is considered to adopt a conformation in which it is perpendicular to the anthracene residue, probably because of  $\pi$ - $\pi$  interactions.<sup>283</sup> Cooling the compound to  $-196^\circ\text{C}$  has a marked effect on the UV absorption spectrum with many red shifts and distortions of the anthracene bands consistent with a change of conformation to one in which the rings are more nearly parallel so that the  $\pi$ -systems can interact. The UV spectrum of the naphthalene analog is much less affected. The perpendicular conformation would actually be favorable for the formation of the compound from its components and may account for the high yield of the mixed cyclophane ( $40\%$ ) along with  $10\%$  furanophane.<sup>283</sup>

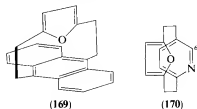
<sup>280</sup> M. Corson, B. M. Foxman, and P. M. Keehn, *Tetrahedron* **34**, 1641 (1978).

<sup>281</sup> C. Wong and W. W. Paudler, *J. Org. Chem.* **39**, 2570, 3618 (1974).

<sup>282</sup> H. E. Wynberg and R. Helder, *Tetrahedron Lett.*, 4317 (1971).

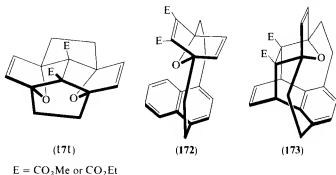
<sup>283</sup> C. B. Shana, S. M. Rosenfeld, and P. M. Keehn, *Tetrahedron* **33**, 1081 (1977).

Among pyridophanes is one example with the pyridine ring perpendicular to a benzene ring and another with pyridine and furan rings at an angle.<sup>284</sup> The latter has structure **170**; the angle between the aromatic planes is 23



and, as is usual in [2.2] cyclophanes, the bond connecting the methylene groups is longer than usual. The furan ring is again only very slightly bent, the pyridine ring suffering enough distortion to increase its thickness by about 0.17 Å. The tilt points the furan oxygen atom at the N—C-6 bond, and the shielding cone of the furan oxygen atom accounts for the shielding experienced by the proton at C-6. Strangely, no indication could be obtained that the furan ring can rotate in this cyclophane, misgivings about apparent rotations in other molecules being engendered thereby.<sup>284</sup>

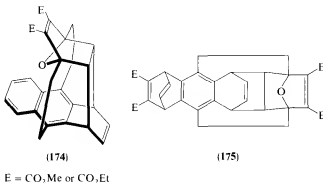
Furanocyclophanes offer some fascinating possibilities for cycloaddition reactions. The furanophane (**155**) adds dimethyl butynedioate to give (presumably) the product of a simple [4 + 2] cycloaddition which, however, immediately undergoes a similar but internal addition leading to **171**. If the initial addition occurs at the less hindered side then evidently the system must undertake a "flip" to bring the activated ethene link into position for the second addition.<sup>273</sup> Wasserman and Kitzing<sup>285</sup> found an essentially similar result in the addition of the acetylenic ester to the cyclophane (**167**), a presumed initial addition giving **172** followed by an internal addition to



<sup>284</sup> J. L. Atwood, W. E. Hunter, C. Wong, and W. W. Paudler, *J. Heterocycl. Chem.* **12**, 433 (1975).

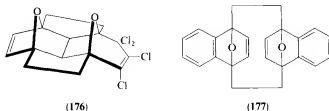
<sup>285</sup> H. H. Wasserman and R. Kitzing, *Tetrahedron Lett.*, 3343 (1969).

the unbridged benzene ring giving **173**. Surprisingly, Wynberg and Helder when they examined the anthracene analog (**169**) found that it was the *nonactivated* bond that engaged in the internal addition; the product would have had structure **174** except that a second, independent addition of acetylene to the terminal benzene ring was superimposed, giving **175**.<sup>282</sup>



In the previous case, of course, the nonactivated double bond did not lie over a benzene ring so had no opportunity to react. In the anthracene (**169**) it is only the central ring—normally the one susceptible to addition—that survives in the product.

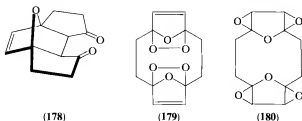
Battiste *et al.*<sup>286</sup> have added tetrachlorocyclopropane instead of an acetylene to the furanophane (**155**) and found once again that initial addition is followed immediately by an internal addition giving **176**, this structure being ascertained by X-ray diffraction. However, when they used benzyne, only intermolecular additions ensued and a mixture containing **177** resulted, notwithstanding the strain that could have been relieved by internal addition.<sup>287</sup> Compound **177** was converted to its tetrahydro derivative which was stable to concentrated sulfuric acid; the stability of similar ethers was noted earlier in Section II,B.



<sup>286</sup> M. A. Battiste, L. A. Kapickak, M. Mathew, and G. J. Palenik, *J. C. S. Chem. Commun.*, 1536 (1971)

<sup>287</sup> L. A. Kapickak and M. A. Battiste, *J. C. S. Chem. Commun.*, 930 (1973)

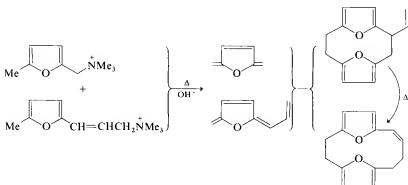
Furanophane **155** adds singlet oxygen and undergoes an intramolecular addition giving **178** if the reaction is conducted in methanol,<sup>288</sup> but in dichloromethane two oxygen molecules add and the product (**179**), being intrinsically unstable, rearranges to the remarkable polyepoxide (**180**).<sup>289</sup>



Similar reactions occur in monocyclic furans (Section VI,B, Part I). Furanophane-oxygen reactions have been used as a starting point for synthetic work.<sup>290</sup>

### 3. [4.2] (2,5)Furanophanes and [4.3] Furanophanes

Nearly all work on cyclophanes has been carried out in the [2.2] series because the members are relatively accessible. This situation may change now that a good method has been discovered for making members of the [4.2] series. The method is a simple extension of the standard procedure in which two suitable quinonoid dienes are cogenerated, but employs a vinyl-ous system as one component (Scheme 65). Two products result, but since



SCHEME 65

<sup>288</sup> H. H. Wasserman and A. R. Doumaux, *J. Am. Chem. Soc.*, **84**, 4611 (1962).

<sup>289</sup> H. H. Wasserman and R. Kitzing, *Tetrahedron Lett.* 5315 (1969).

<sup>290</sup> T. J. Katz, V. Balogh, and J. Schulman, *J. Am. Chem. Soc.*, **90**, 734 (1968).

one isomerizes to the other above 130°C yields about 24% are easily attainable. Hydrogenation supplies the [4.2] cyclophane itself. Acid hydrolysis yields the corresponding diones, and the Paal-Knorr cyclization then gives the corresponding pyrroles.<sup>291</sup>

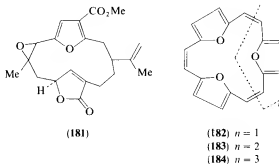
Pukalide, a compound isolated from the soft octocoral *Sinularia abrupta*, is a remarkable natural product with structure **181** containing what amounts to a [4.3] furanophane ring system, one furan ring being in the form of a butenolide group. No synthetic compound is known that even approximates pukalide<sup>292</sup> but zexbrevin is a similar 3-furanone obtained from a shrub.<sup>130</sup>

### C. ANNULENES

Furans have played a considerable part in the development of annulene chemistry, largely because they provide suitable building blocks for generating macrocyclic rings.

#### 1. Epoxyannulenes: 2,5-Linked Furans

Elix converted 5-chloromethylfuran-2-carbaldehyde to a phosphonium salt and treated it with lithium ethoxide in dimethylformamide to generate a phosphorane. This condensed with itself and produced the now well-known red trifuran (**182**), a tetrafuran (**183**) in two (*E,Z*)-configurations (one violet-black, the other violet), and the pentafulan (**184**), also in two configurations. Since the chloromethylfuran is obtained from sucrose and hydrogen chloride the synthesis is remarkably simple, although the yields are low.<sup>293</sup>

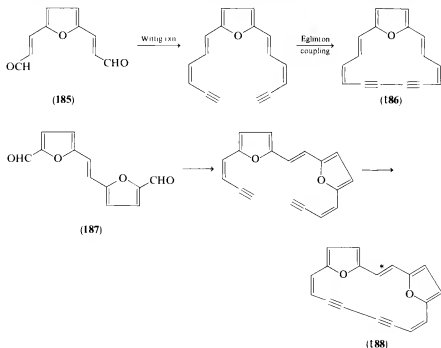


<sup>291</sup> P. S. Hammond and D. T. Longone, *Tetrahedron Lett.*, 415 (1978).

<sup>292</sup> M. G. Missakian, B. J. Burrenson, and P. J. Scheuer, *Tetrahedron* **31**, 2513 (1975).

<sup>293</sup> J. A. Elix, *Chem. Commun.*, 343 (1968).

The furan oxygen can play no part in the periphery, and such compounds behave in the same way as their parent nonoxidic systems; the trifuran is an [18] annulene and is aromatic (i.e., diatropic) whereas the tetrafurans are [24] annulenes and are paratropic, their external protons resonating at rather high fields ( $\sim \delta$  5) compared with simple vinylfurans. As [30] annulenes, the pentafurans have presumably passed beyond the bounds of Hückel aromaticity. Japanese workers have discovered that, far from invalidating the Hückel aromaticity rule, the epoxy links sharpen the difference between aromatic and non- or antiaromatic members of the series, as judged by spectroscopic criteria.<sup>294,295</sup> The compounds were made by standard methods; for example, **186** from the furan dialdehyde (**185**)<sup>296</sup> and **188**<sup>297</sup> from the bisfuran dialdehyde (**187**), as shown in Scheme 66. Annulene (**188**) is obtained only with the starred bond trans even when prepared from **187** in its cis form. Moreover, the large ring in **188** allows rotation of the bisfuran



SCHEME 66

<sup>294</sup> H. Ogawa, J. Mukae, Y. Taniguchi, and H. Kato, *Tetrahedron Lett.*, 4929 (1978).

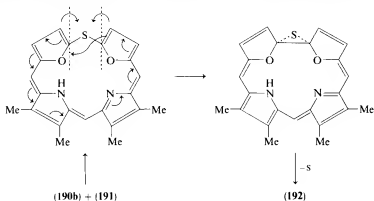
<sup>295</sup> H. Ogawa, N. Shimojo, H. Kato, and H. Saikachi, *Tetrahedron* **30**, 1033 (1974).

<sup>296</sup> T. M. Cresp, M. V. Sargent, and P. Vogel, *J. C. S. Perkin I*, 37 (1974).

<sup>297</sup> H. Saikachi, H. Ogawa, and K. Sato, *Chem. Pharm. Bull.* **19**, 97 (1971).

part as a rigid unit, and the NMR spectrum shows temperature-variable line-broadening.<sup>294</sup> The furan ring in such annulenes is roughly equivalent to a cumulene grouping, so that **186**, for example, is slightly more paratropic than **189**.<sup>294</sup>

Johnson and his colleagues<sup>298</sup> have concerned themselves with annulenes of the porphin and corrole types in which furan as well as pyrrole segments participate. The MacDonald porphin synthesis (HBr in air) applied to 2,2'-bisfuran-5,5'-dicarbaldehyde (**190a**) and a suitable dipyrrole (e.g., **191**) did give **192** but in rather poor yield. Much better results were secured by using as the furan component the 2,2'-thiobisfuran (**190b**) in which disrotatory cyclization under orbital symmetry control could be followed by cheletropic extrusion of sulfur thus locking the system (Scheme 67). Such



SCHEME 67

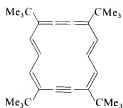
annulenes showed a strong, induced diamagnetic ring current, and those with two or more furan nuclei proved to be much stronger bases than had been expected. If the condensations are prolonged, new ring systems (**193**) containing two furan and three pyrrole rings begin to emerge. They are related to the sapphyrins, and can be made rationally by condensing the difuran (**190a**) with a suitable three-pyrrole partner; they exist as single isomers, exhibit strong Soret bands, and behave as strongly aromatic species. On the other hand, they do not form metal derivatives in the way that oxaporphins do.<sup>298</sup> Porphins with *meso*-furyl substituents have been described.<sup>299</sup> Annulenes such as **194** containing a sulfur link are known but do not support diamagnetic ring currents, although the electron count is correct. The system may be buckled by the sulfur atom.<sup>300</sup>

<sup>298</sup> M. J. Broadbent, R. Grigg, and A. W. Johnson, *J. C. S. Perkin I*, 1124, 2111 (1972).

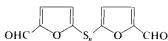
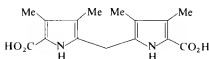
<sup>299</sup> M. Mometeau, B. Looek, and E. Bisagni, *J. Heterocycl. Chem.*, **16**, 191 (1979).

<sup>300</sup> T. M. Cresp and M. V. Sargent, *J. C. S. Perkin I*, 1786 (1973).

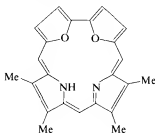




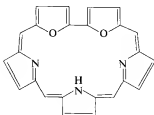
(189)

(190a)  $n = 0$ (190b)  $n = 1$ 

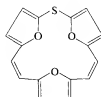
(191)



(192)



(193)



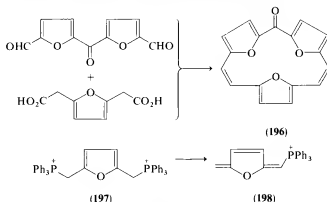
(194)

## 2. Epoxyannulenones and Epoxyannulenium Salts

Furan-containing annulenes with a carbonyl group in the ring have proved especially interesting. Whereas the ketone (195) is, strictly speaking, a cyclophane, it is mentioned here because the ring seems small to contain an allene grouping.<sup>301</sup> Genuine annulenones have an odd number of atoms in the periphery and their syntheses follow standard procedures as far as their furan rings are concerned. In preparing the first [17] annulenone, Cresp and Sargent effected a double Perkin condensation between a difuran dialdehyde and furan-2,5-diacetic acid to obtain a trifuran (196), as in Scheme 68. Wittig condensations with the diposphonium salt (197) are confused by the tendency of the salt to eliminate phosphine giving the

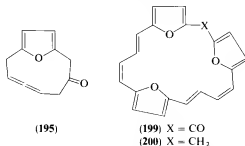
<sup>301</sup> P. J. Garratt, K. C. Nicolson, and F. Sondheimer, *J. Org. Chem.* **38**, 864 (1973).

2,5-bismethylenefuran (198) so that the use of this particular component is excluded; otherwise standard techniques are satisfactory.<sup>302</sup>



SCHEME 68

The carbonyl group of annulenone (196) is unreactive except toward lithium aluminium hydride promoted by aluminium chloride, which reduces it to the methylene group. Cresp and Sargent also describe the larger ring system in the ketone (199) and point out that, although the compound does show low-field shifts in the internal protons at positions 8 and 15, this cannot be a sign of paratropicity because the corresponding methylene compound (200) shows *greater* low-field shifts. The ring size is now beyond the operation of the Hückel rule. They ascribe the shifts to steric compression and to deshielding effects emanating from the closely held furan oxygen atom which approaches the internal protons at positions 8 and 15 rather closely.<sup>302</sup>

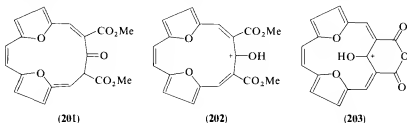


A related series of annulenones but with the carbonyl group opposite to the furan rings has been investigated by Ogawa and co-workers<sup>303</sup> who

<sup>302</sup> T. M. Cresp and M. V. Sargent, *J. C. S. Perkin I*, 2961 (1973), 2145 (1974).

<sup>303</sup> H. Ogawa and I. Tabushi, *Tetrahedron Lett.*, 5065 (1973), H. Ogawa, M. Yoshida, and H. Saikachi, *ibid.*, 153 (1972).

used furan units because the oxide links in effect replace hydrogen atoms and so remove interfering collisions. They also rigidify frameworks that might otherwise be inconveniently flexible. The annulenone (**201**) from the requisite difurandialdehyde and acetonedicarboxylic ester exhibited spectacular colorations in sulfuric acid, by turns blue, purple, and red. The PMR spectrum shows that the blue corresponds to the annulenium ion (**202**), which is strongly diatropic, whereas the final red corresponds to anhydride (**203**) in



which the anhydride ring enforces planarity on the ring system and forces the protonated carbonyl oxygen atom to turn inward. Other studies have extended these results to [15] homoannulenium ions<sup>303</sup> and to a [5] annuleno [15] annulenone ring system.<sup>304</sup> Such rings are large enough to accommodate (*E,Z*)-isomerism with ease, and the chief workers offer a joint paper on the subject.<sup>305</sup>

### 3. Annulenofurans: 3,4-Linked Furans

Furanoid oxaannulenes are annulenes in which the oxygen atom of the furan ring is necessarily part of the periphery.<sup>306</sup> The best-known furanoid oxaannulene is isobenzofuran (**205**), although this compound is properly regarded as a combination of a furan nucleus with a butadiene segment added and not as an oxaannulene.<sup>307</sup> Comments associated with Scheme 70 are also pertinent. Ring [*c*] furans have been reviewed.<sup>307a</sup>

One of the simplest and smallest rings under this heading is 3-oxabicyclo-[3.2.0]hepta-1,4,6-triene (**206**), a compound obtained by heating *cis*- or *trans*-1,2-divinyloxiran.<sup>308</sup> It is probably a truly antiaromatic 8- $\pi$  system for it has a complex UV spectrum quite unlike that of furan, its protons

<sup>304</sup> H. Ogawa and A. Chisaka, *Tetrahedron Lett.*, 4811 (1978).

<sup>305</sup> H. Ogawa, H. Kato, N. Ibi, T. M. Cresp, and M. V. Sargent, *Tetrahedron Lett.*, 3889 (1974).

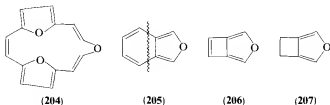
<sup>306</sup> H. Ogawa, M. Kubo, and H. Saikachi, *Tetrahedron Lett.*, 4859 (1971); H. Ogawa and M. Kubo, *Tetrahedron* **29**, 809 (1973).

<sup>307</sup> E. Chacko, J. Bornstein, and D. J. Sardella, *J. Am. Chem. Soc.* **99**, 8248 (1977).

<sup>307a</sup> N. Friedrichsen, *Adv. Heterocycl. Chem.* **26**, 135 (1980).

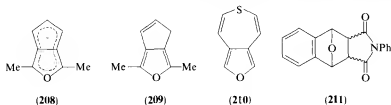
<sup>308</sup> K. P. C. Vollhardt and R. G. Bergmann, *J. Am. Chem. Soc.* **94**, 8950 (1972).

adjacent to oxygen resonate at a rather high field (about  $\delta$  6.1), and it is a very sensitive substance (e.g., to oxygen and to glc columns). Hydrogenation readily gives the dihydro derivative (**207**) which behaves like an ordinary furan.<sup>309</sup>



The next higher annulene is known in the form of the 2-oxapentalenyl anion (**208**), and has been prepared from 2,5-dimethylfuran-3-propanoic acid via **209** which was treated with butyllithium. The simplicity of the PMR spectrum is consistent only with a fully delocalized electronic arrangement, i.e., the ion is essentially free from bonding with lithium. However, it is probably less aromatic than the corresponding sulfur heterocycle since its methyl protons resonate at a higher field, thus suggesting that the ring current is not wholly able to counteract the effect of the increased negative charge. The ion reacts as a carbanion at position 4 with deuterium oxide, iodomethane, and benzophenone.<sup>310</sup>

The larger system in **210** is of interest because it adds *N*-phenylmaleimide so as to extrude sulfur and give the adduct (exo/endo mixture) (**211**) identical



with that from **205**.<sup>311</sup> Much larger rings, such as that in **212**, have been examined particularly by Sondheimer and his colleagues.<sup>312</sup> Syntheses usually start from the dialdehyde (**149**), itself conveniently obtained from the now commercially available furan-3,4-dicarboxylic acid.<sup>266</sup> The aldehyde groups are condensed with Wittig reagents, which often contain any acetylenic residues that may be necessary. The ring is closed by acetylenic

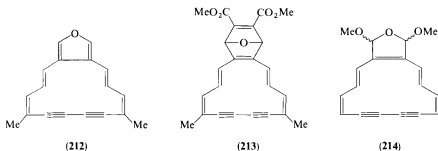
<sup>309</sup> R. G. Bergmann and K. P. C. Vollhardt, *J. C. S. Chem. Commun.*, 214 (1973).

<sup>310</sup> T. S. Cantrell and B. L. Harrison, *Tetrahedron Lett.*, 1299 (1969).

<sup>311</sup> R. H. Schlessinger and G. S. Pinticello, *Tetrahedron Lett.*, 4361 (1969).

<sup>312</sup> P. J. Beety, R. T. Weavers, and F. Sondheimer, *Angew. Chem., Int. Ed. Engl.* **13**, 138 (1974), R. T. Weavers and F. Sondheimer, *ibid.*, 139, 141.

coupling. A series of dehydroannulenes have been made in this manner and their aromaticity assessed by the tendency of the furan part to add dimethyl butynedioate (e.g., **212** converted to **213**). The rate constants for addition were determined and dehydro [12] annulene[c]furan and dehydro [16] annulene[c]furan were found to add more slowly, while the [14] and [18] annulenofurans added more quickly than did a very similar open chain analog.<sup>313</sup> When the furan electrons are included, the results are consistent with Hückel aromaticity. Whereas annulenofurans like **212** can be looked upon as protected annulene dialdehydes, attempts to expose the two aldehyde functions have failed. The corresponding 2,5-dihydro-2,5-dihydroxyfurans are readily obtained, for example, as the diacetates by the use of lead(IV) acetate; but the system is so resistant to ring opening that treatment with sodium methoxide produces the dimethyl ether (**214**), an unprecedented finding.<sup>266</sup>



[1,2-*c*:5,6-*c*]Cyclooctabisfuran, an annulene with two peripheral (furanoid) oxygen atoms, has also been prepared.<sup>314</sup>

#### 4. Furotropones: 2,3-Linked Furans

The so-called furotropones (**215**), first described in 1968, might also be classified as annulenones. The synthesis of **215a** by condensation of the furan dialdehyde (**149**) with acetone in base seems very simple, but the condensation has to be of short duration so that undue hydrolysis of the furan (a doubly vinylogous ester) can be avoided. Moreover, it is crucial that the angle between the aldehyde functions is greater than that in the benzene series.<sup>315</sup> Thus, the angle is large enough to fit exactly into the nascent seven-membered ring and also large enough to reduce the tendency of the aldehyde groups to react with each other as they do in *o*-phthalaldehyde,

<sup>313</sup> R. H. Wightman, T. M. Cresp, and F. Sondheimer, *J. Am. Chem. Soc.* **98**, 6052 (1976).

<sup>314</sup> J. A. Elix, M. V. Sargent, and F. Sondheimer, *J. Am. Chem. Soc.* **89**, 5080 (1967).

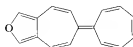
<sup>315</sup> M. J. Cook and E. J. Forbes, *Tetrahedron* **24**, 4501 (1968).

which fails to give the corresponding benzotropone. Use of deuterated acetone gives the labeled **215b**. The IR absorption at  $1599\text{ cm}^{-1}$  is ascribed to the carbonyl group and thought to indicate a lesser "aromaticity" than in the tropone itself; the carbonyl group reacts with hydroxylamine to give an oxime (tropone gives aminotropone instead). On the whole the compound does not behave as a  $10\pi$ -electron aromatic annulenone, although sulfuric acid does appear to protonate the carbonyl group (rather than the furan ring), which should lead to an annulenium ion.<sup>315</sup>

Ketenes react at the carbonyl group of **215a** to eliminate carbon dioxide and produce the more extended conjugated system (as in **216** obtained from a cycloheptatrienylidene ketene.)<sup>316</sup> Reduction with metal hydride removes the carbonyl oxygen and induces coupling of two residues at the 4-position.<sup>317</sup> Addition of dienophiles is not observed in the parent system, but the furan part of the dibenzotropone (**217**) readily adds quinones and other such addenda.<sup>318</sup>

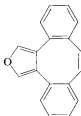


(215a) R = H  
(215b) R = D



(216)

The 2,3-dialdehyde of furan reacts with ketones in syntheses of furotropones similar to **218a**. Deuterium analogs (e.g., **218b**) are available from labeled dimethylformamide used to prepare the furan starting material.<sup>319</sup> Metal hydride reagents afford (tautomeric?) cycloheptatrienes (**219**), but



(217)



(218a) R = H  
(218b) R = D



(219)

<sup>316</sup> T. Asao, N. Morita, and K. Kato, *Heterocycles* **11**, 287 (1978).

<sup>317</sup> M. El Borai, R. Guilard, P. Fournari, Y. Dusausoy, and J. Protas, *Bull. Soc. Chim. Fr.*, 75 (1977).

<sup>318</sup> T. Sasaki, K. Kanamatsu, K. Tizuka, and I. Ando, *J. Org. Chem.* **41**, 1425 (1976).

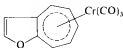
<sup>319</sup> M. El Borai, R. Guilard, and P. Fournari, *Bull. Soc. Chim. Fr.*, 1383 (1974).

reduction can be limited to the alcohol stage whereafter acids afford a complex (**221**) defined by X-ray analysis.<sup>317</sup> Tropones like **222** are also known; they react with ketenes in the same way as does **215a**.<sup>316</sup>

A ditropolonofuran, utahin, occurs naturally.<sup>320</sup>



(220)



(221)



(222)

## VI. Structure, Physicochemical Properties, and Reactivity

The previous review<sup>1</sup> of furans contained no comparable section; this one is added because chemists no longer devise syntheses or study reaction possibilities without regard to size and shape or activation and electronic interactions. On the other hand we cannot delve very deeply into these subjects; they are too extensive. Several excellent reviews deal with specific aspects of the physical chemistry of the five-membered heterocycles. A general review has been published in Russian.<sup>321</sup>

### A. STEREOCHEMISTRY

#### 1. Shape

Furan and its congenors are flat like benzene but are roughly (regular) pentagonal in shape. Accurate values for bond lengths (diagram **223**) and bond angles (diagram **224**) were obtained by microwave methods utilizing  $[2-^{13}\text{C}]\text{furan}$ ,  $[3-^{13}\text{C}]\text{furan}$ , and  $[^{18}\text{O}]\text{furan}$  and published in 1962 by Bak *et al.*<sup>322</sup> Microwave spectra of methylfurans are also available.<sup>323</sup> An electron diffraction study of bromo- and chlorofurans shows that the C—Br distance for 3-bromofuran (1.853 Å) is a little larger than that for 2-bromofuran (1.840 Å).<sup>324</sup> Numerous complex structures containing a furan

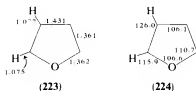
<sup>320</sup> K. H. Baggeley and T. Norin, *Chem. Commun.*, 233 (1968).

<sup>321</sup> I. A. Abronin and G. M. Zhidomirov, *Khim. Geterotsikl. Soedin.*, 3 (1977).

<sup>322</sup> B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. Rastrup-Andersen, and M. Schottlander, *J. Mol. Spectrosc.*, **9**, 124 (1962).

<sup>323</sup> W. G. Norris and L. C. Krisher, *J. Chem. Phys.*, **51**, 403 (1969); T. Ogata and K. Kozima, *Bull. Chem. Soc. Jpn.*, **44**, 2344 (1971).

<sup>324</sup> G. H. Scherbak, L. V. Vilkov, N. I. Sadova, and Yu. A. Boiko, *Zh. Strukt. Khim.*, **20**, 530 (1979).



ring have been determined by X-ray diffraction, most often as part of structure determinations of natural products. As the furan ring is almost never the focus of attention in such studies we merely list references to examples taken more or less at random so as to illustrate a variety of substitution patterns: 3-monoalkyl,<sup>324a-335</sup> 2,3-dialkyl,<sup>336</sup> 2,3,4-trialkyl,<sup>336a</sup> 2-acyl-3-alkyl,<sup>337</sup> 3-bromo-2-formyl,<sup>338</sup> 2,4-diacyl-3-alkyl,<sup>339,340</sup> 3,4-diacyl-2,5-diakyl,<sup>340a</sup> and 2-alkenyl-5-nitro.<sup>341,342</sup> The 2,5-disubstituted furans in the cyclophane series are of special interest due to distortion.<sup>280,284</sup> We should

<sup>324a</sup> D. W. Knight and G. Pattenden *J. Chem. Soc. Perkin I*, 635, 641 (1975).

<sup>325</sup> W. Hofheinz and P. Schonholzer, *Helv. Chim. Acta* **60**, 1367 (1977).

<sup>326</sup> J. Fayos, M. Martinez-Ripoll, M. Paternostro, F. Piozzi, B. Rodriguez, and G. Savona, *J. Org. Chem.* **44**, 4992 (1979).

<sup>327</sup> E. Fujita, I. Uchida, and T. Fujita, *J. C. S. Perkin I*, 1547 (1974).

<sup>328</sup> G. Ferguson, W. C. Marsh, R. McCrindle, and E. Nakamura, *J. C. S. Chem. Commun.*, 299 (1975).

<sup>329</sup> V. P. Gullo, I. Miura, K. Nakanishi, A. F. Cameron, J. D. Connolly, F. D. Duncanson, A. E. Harding, R. McCrindle, and D. A. H. Taylor, *J. C. S. Chem. Commun.*, 345 (1975).

<sup>330</sup> D. P. Chakraborty, P. Bhattacharyya, S. P. Bhattacharyya, J. Bordner, G. L. A. Hennessee, and B. Weinstein, *J. C. S. Chem. Commun.*, 246 (1979).

<sup>331</sup> K. Kitazawa, A. Ogiso, S. Takahashi, A. Sato, M. Kurabayashi, H. Kuwano, T. Hata, and C. Tamura, *Tetrahedron Lett.*, 1117 (1979).

<sup>332</sup> G. Henkel, H. Diercks, B. Epe, and A. Mondon, *Tetrahedron Lett.*, 3315 (1975).

<sup>333</sup> H. Wagner, R. Seitz, V. M. Chari, H. Lotter, and W. Herz, *Tetrahedron Lett.*, 3039 (1977).

<sup>334</sup> L. Brehm, O. J. R. Hodder, and T. G. Halsall, *J. Chem. Soc. C*, 2529 (1971).

<sup>335</sup> J. Polonsky, Z. Varon, B. Arnoux, C. Pascard, G. R. Pettit, and J. M. Schmidt, *J. Am. Chem. Soc.* **100**, 7731 (1978).

<sup>336</sup> R. Kazlauskas, P. T. Murphy, R. J. Wells, J. J. Daly, and P. Schonholzer, *Tetrahedron Lett.*, 4951 (1978).

<sup>336a</sup> P. W. Jennings, S. K. Reeder, J. C. Hurley, C. N. Caughlan, and G. D. Smith, *J. Org. Chem.* **39**, 3392 (1974).

<sup>337</sup> J. Lopez de Lerma, S. Garcia-Blanco, and J. G. Rodriguez, *Tetrahedron Lett.* **20**, 1273 (1980).

<sup>338</sup> B. Roques, S. Combrisson, C. Riche, and C. Pascard-Billy, *Tetrahedron* **26**, 3555 (1970).

<sup>339</sup> K. C. Joshi, P. Singh, R. T. Pardasani, A. Pelter, R. S. Ward, and R. Reinhardt, *Tetrahedron Lett.*, 4719 (1978).

<sup>340</sup> T. J. Petcher, H.-P. Weber, and Z. Kis, *J. C. S. Chem. Commun.*, 1061 (1972).

<sup>340a</sup> L. Fanfani and P. F. Zanazzi, *Atti. Accad. Naz. Lincei Cl. Sci. Fis., Mat. Nat., Rend.* **45**, 158 (1968).

<sup>341</sup> D. Geisbacher, A. Juracek, and J. Kovac, *Collect. Czech. Chem. Commun.* **44**, 1984 (1979).

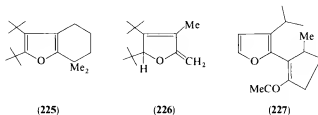
<sup>342</sup> A. Kuca and T. N. Polynova, *Dokl. Akad. Nauk SSSR* **245**, 397 (1979).



perhaps also list some butenolides,<sup>324a,343,344</sup> and tetrone acids and related compounds<sup>168,345,346</sup> and, in conclusion, two furan-3-ones.<sup>133,347</sup> The reader is directed to other reviews for a more extensive listing of naturally occurring butenolides.<sup>72,73,134</sup>

The geometry of the furan nucleus has been found ideal for building up annulene systems as explained in Section VI,C and as spelled out diagrammatically by Ogawa and Chisaka in connection with bridged annulenone rings.<sup>304</sup> Apart from the suitability of the bond angles provided by the furan ring, the "small" size of its oxygen atom allows it to occupy positions in the smaller annulenes in place of sterically hindered methine groups. For the same reason the furan ring in a cyclophane can sometimes rotate where a benzene, pyrrole, or even thiophene ring cannot.

In comparing furan with benzene chemistry it is necessary to remember that geometrical difference between a five- and a six-membered ring will have some effect. Thus, adjacent substituents on a furan ring are further apart than on a benzene ring so that "ortho" effects, though observed in furan chemistry, are relatively small.<sup>348-350</sup> It is even possible to observe ortho-di-*t*-butylation by simple electrophilic substitution giving compounds such as **225**; steric interaction is betrayed by the tendency of the product (**226**) to be nonaromatic.<sup>351</sup> However, there is enough steric interaction in **227**, a typical constituent of the so-called geranium bourbon essence (ex *Pelargonium roseum*) to prevent the rings from attaining coplanarity and developing normal UV intensities, although there is not enough to affect the wavelengths greatly.<sup>352</sup>



<sup>343</sup> D. Uemura, C. Katayama, and Y. Hirata, *Tetrahedron Lett.*, 283 (1977).

<sup>344</sup> J. A. Pettus, R. M. Wing, and J. J. Sims, *Tetrahedron Lett.*, 41 (1977).

<sup>345</sup> M. J. Begley, D. R. Gedge, D. W. Knight, and G. Pattenden, *J. C. S. Perkin I*, 77 (1979).

<sup>346</sup> D. M. Gedge and G. Pattenden, *J. C. S. Perkin I*, 89 (1979).

<sup>347</sup> K. Ando, H. Sasaki, T. Hosokawa, Y. Nawata, and Y. Itaka, *Tetrahedron Lett.*, 887 (1975).

<sup>348</sup> C. Dell'Erba, A. Guareschi, and D. Spinelli, *J. Heterocycl. Chem.*, 4, 438 (1967); D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J. C. S. Perkin II*, 1632 (1974).

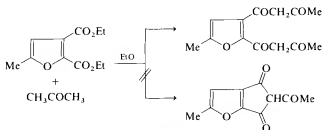
<sup>349</sup> C. Clementi, P. Linda, and M. Vergoni, *Tetrahedron Lett.*, 611 (1971).

<sup>350</sup> R. G. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Lett.*, 3857 (1972).

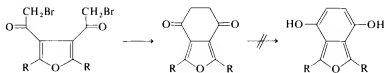
<sup>351</sup> H. Wynberg and U. E. Wiersum, *Tetrahedron Lett.*, 3619 (1975).

<sup>352</sup> C. Gianotti and H. Schwang, *Tetrahedron* 24, 2055 (1968).

The angles at which substituents project from the ring is larger in furan than in benzene with consequences for the ease of ring fusion. Scheme 69



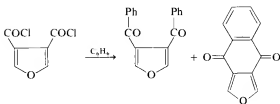
shows that, in contrast to benzene chemistry, closure to a five-membered ring is not favored if it produces fusion with a furan ring.<sup>353</sup> A contrasting example is provided by the synthesis of **215a** from furan-2,3-dicarbaldehyde and acetone in base, since the furan ring is seen to accept formation of a (fused) seven-membered ring whereas a benzene ring fails to do so.<sup>315</sup> A particularly interesting result has been obtained by Ghera, Gaoni, and Perry who cyclized a 3,4-bis(bromoacetyl)furan with zinc-copper couple to obtain a dihydroisobenzofuranquinone in about 50% yield (Scheme 70). Evidently



there was no marked barrier to annelation with a six-membered ring, yet the product was unusually resistant to dehydrogenation to the quinone by DDQ or chloranil and did not enolize readily, showing no UV change on addition of acid or base. However, the trimethylsilyl ether of the dienol could be obtained normally.<sup>354</sup> The Friedel-Crafts reaction between a furan-3,4-dicarboxylic acid chloride and benzene also betrays a ring-size preference. In the benzene series (i.e., with a phthaloyl chloride) such reactions mainly give five-membered rings (phthaleins) although 2-benzoylbenzoic acids or the derived anthraquinones can also be obtained. But the furan only gives a quinone (Scheme 71) accompanied by a dibenzoylfuran, the two acids

<sup>353</sup> W. A. Mosher and L. A. Blanchard, *J. Heterocycl. Chem.* **9**, 949 (1972).

<sup>354</sup> E. Ghera, Y. Gaoni, and D. H. Perry, *J. C. S. Chem. Commun.*, 1034 (1974).



SCHEME 71

chloride groupings acting entirely independently.<sup>355</sup> Moreover furans bearing lithium and halogen on adjacent atoms show no tendency to collapse into an analog of benzyne (Section IV,A, Vol. 30). The effect of fusing a furan ring to a cyclobutene ring was discussed earlier (p. 320).<sup>309</sup>

A geometrical consideration of a different kind appears in the relative "stiffness" of the furan ring. When constrained, as in some cyclophanes, a benzene ring bends without losing its aromatic character. But in cyclophanes with both a benzene ring and a furan ring, it is the benzene ring that bends, the furan ring being hardly affected. Similarly, pyridine and naphthalene rings bend in preference to a furan ring (Section V,B).<sup>280,284</sup> The stiffness of the furan ring has already been alluded to (p. 298) in connection with gramacrane-type terpene furans where it is thought to prevent the 10-membered ring from attaining the correct conformation for the Cope rearrangement usually observed.<sup>236</sup>

## 2. Rotational Isomerism of Acyl and Other Derivatives

That 2-acylfurans (and thiophenes, etc.) exist in two distinct conformations was discovered by Allen and Bernstein in 1955 and has always been understood in terms of an equilibrium between the oxygen-cis or *Z* and oxygen-trans or *E* forms, (228) and 229, as shown for furfuraldehyde. (Cis and trans and syn and anti terms are found in the literature applied in one sense by some authors and in the opposite sense by others.) The identification of the isomers has been very troublesome. Several authors give the main references.<sup>356-358</sup> Microwave measurements<sup>359</sup> on furfuraldehyde show that in the vapor phase the oxygen-cis conformer is the more stable but only by

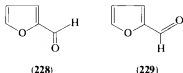
<sup>355</sup> L. M. Gomes, C. R. Acad. Sci., Ser. C **278**, 1055 (1974).

<sup>356</sup> R. J. Abraham and T. M. Sivers, *Tetrahedron* **28**, 3015 (1972).

<sup>357</sup> J. M. Angelelli, A. R. Katritzky, R. F. Pinzelli, and R. D. Topsom, *Tetrahedron* **28**, 2037 (1972).

<sup>358</sup> I. G. John and L. Radom, *J. Am. Chem. Soc.* **100**, 3881 (1978).

<sup>359</sup> F. Monning, H. Driezler, and H. D. Rudolph, *Z. Naturforsch.*, A **20A**, 1323 (1965); B. R. Larsen, T. Nicolaisen, and J. T. Nielsen, *Acta Chem. Scand.* **26**, 1736 (1972).



about 4 kJ/mol, and it is now accepted that the equilibrium is strongly dependent upon the medium; in the vapor phase or in nonpolar solvents the oxygen-trans species is the main one, whereas the oxygen-cis species is the more important in the more polar solvents as demonstrated by the variation in the stereospecific long range couplings between the formyl proton and the ring protons.<sup>356</sup> This confirmed conclusions based upon the crystal structure of 3-bromofuran-2-carbaldehyde,<sup>338</sup> and disposes of arguments based upon chemical shifts, which are insecure because a change in conformation affects both the internal electronic contribution and the magnetic anisotropy at the 3-position.

Another source of confusion had its origin in the twin carbonyl stretching band found in the IR spectrum of furfuraldehyde. The double peak was assumed to arise from the two species, oxygen-cis and oxygen-trans, even though the results were difficult to fit to those revealed by other physical probes. The same phenomenon occurs in the thiophene series where it was eventually traced to Fermi resonance between the carbonyl and the C(5)—H vibrations.<sup>360</sup> That Fermi resonance is also responsible in the furan series has been demonstrated by showing that there is only one carbonyl band in furfuraldehyde when position 5 is deuterated.<sup>361</sup>

More recently, <sup>13</sup>C-NMR studies have been used to investigate rotational isomerism. At lower temperatures line broadening is observable and below -60°C furfural in dichloromethane shows two C-3 and two C=O resonances the relative intensities and chemical shifts of which suggest a ratio of oxygen-cis to oxygen-trans isomers of 5:1, in conformity with the earlier work.<sup>362</sup>

By comparison, very little has been done with furan-3-carbaldehyde.<sup>363</sup> However, there have been several studies of 2-acylfurans other than the aldehyde. Steric effects are believed to be vanishingly small in the rotational phenomena of furfural, the free energy differences being somewhere near 4 kJ/mol and the energy barrier near 45 kJ/mol. With groups larger than formyl some degree of steric constraint is likely and may account for the variations in conformation shown by long range couplings in the series of

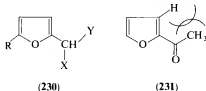
<sup>360</sup> H. Lumbroso, D. M. Bertin, and P. Cagniant, *Bull. Soc. Chim. Fr.*, 1720 (1970); C. Andrieu, R. Pinel, and Y. Mollier, *ibid.*, 1314 (1971).

<sup>361</sup> D. J. Chadwick, G. D. Meakins, and R. L. Snowden, *J. C. S. Chem. Commun.*, 742 (1972).

<sup>362</sup> D. J. Chadwick, G. D. Meakins, and E. E. Richards, *Tetrahedron Lett.*, 3183 (1974).

<sup>363</sup> M. C. Fournie-Zaluski and B. Roques, *Tetrahedron Lett.*, 4909 (1970).

furans (230).<sup>364</sup> Steric factors may also account for the rotamer ratio near unity for 2-acetylfuran since the methyl group will tend to collide with the hydrogen at position 3 in what is usually the more favorable oxygen-cis form corresponding to 231. Several methods have been used to determine



this ratio, but none is simpler and more convincing than that based on the nuclear Overhauser effect, which clearly distinguishes the rotamer with the methyl close to the 3-hydrogen atom.<sup>365</sup> At lower temperatures the <sup>13</sup>C spectra show the cis isomer to be increasingly important; and this powerful technique is capable of detecting rotational isomerism when many methods fail (e.g., with *t*-butyl 2-furoate which shows line broadening as the temperature is reduced).<sup>362</sup> A similar study of the acid fluoride of 2-furoic acid shows that this compound also exists as discrete rotamers; the fluorine spectrum shows the appropriate two lines that coalesce as the temperature is reduced and then separate again into pairs of signals.<sup>366</sup> Several LIS studies have also been made, although the technique is not without its drawbacks.<sup>362,367</sup>

From CNDO/2 calculations the expected distorted planar conformation can be deduced for 2-phenyl furan.<sup>368</sup> The <sup>1</sup>H-NMR spectra indicate that derivatives of 2-(2-furyl)pyrrole (232) take up a nearly coplanar conformation, with the two heteroatoms syn oriented.<sup>369</sup> Another such study included extended Hückel MO calculations that confirmed a general preference for syn orientation and showed that the barriers to change from syn to anti decrease sharply from bifurans to bithiophenes in the order of attachment 2,2' > 2,3' > 3,3'.<sup>370</sup> Studies of furan analogs of (*E*)-stilbene by dipole moment methods<sup>371</sup> and by NMR methods<sup>372</sup> suggest that the rings are tilted to accommodate each other, whereas strong shielding of the 3-proton in

<sup>364</sup> G. C. Brophy, P. J. Newcombe, and R. K. Norris, *Aust. J. Chem.* **30**, 357 (1977).

<sup>365</sup> K.-I. Dahlqvist and A.-B. Hörnfeldt, *Tetrahedron Lett.*, 3837 (1971).

<sup>366</sup> D. Chadwick, *Tetrahedron Lett.*, 679 (1975).

<sup>367</sup> C. Montaudo, S. Caccamese, V. Librando, and P. Maravigna, *Tetrahedron* **29**, 3915 (1973); S. Nagata, T. Yamabe, K. Yoshikawa, and H. Kato, *ibid.*, 2545.

<sup>368</sup> V. Galasso and G. De Alti, *Tetrahedron* **27**, 4547 (1971).

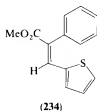
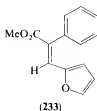
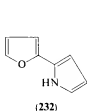
<sup>369</sup> B. A. Trofimov, V. K. Voronov, A. I. Mikhaleva, R. I. Polovnikov, R. N. Nesterenko, and M. V. Sigalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2372 (1979).

<sup>370</sup> V. Galasso and N. Trinajstić, *Tetrahedron* **28**, 4419 (1972).

<sup>371</sup> S. Gruttadauria and G. C. Pappalardo, *Bull. Chem. Soc. Jpn.* **48**, 1681 (1975).

<sup>372</sup> S. Fisichella, G. Mineri, G. Scarlata, and D. Sciotto, *Tetrahedron* **31**, 2445 (1975).

the furan nucleus by the phenyl group demands the 5-*cis* conformation shown in **233**; because the thiophene analog reveals no shielding, the *s-trans* arrangement (**234**) is likely. In the (*Z*)-configurations neither heterocycle



exhibits shielding.<sup>372</sup> Differences between the two heterocycles are seldom so marked. In explanation, it is suggested that the oxygen atom may be repelled by  $\pi$ -electrons in the benzene ring, a view that might also account for the fact that in 2-carbaldehydes the *cis* isomer is much more abundant for the thiophene than for the furan.<sup>372</sup>

In a comprehensive paper, John and Radom<sup>358</sup> describe the results of an *ab initio* MO study. The furans considered include the parent compound and monosubstituted furans with alkyl, hydroxymethyl, fluoromethyl, amino, hydroxyl-, methoxyl, formyl, acetyl, carboxamide, carboxyl, and nitroso groups at positions 2 or 3. Three conformations were chosen for detailed study: the *cis* or *syn*, the *trans* or *anti*, and the perpendicular. The results confirm geometries outlined above and disclose further subtleties for which there is no analogy in benzene chemistry. For example, 3-substituted furans tend to favor the conformation in which a single bond X—Y eclipses the 2,3-bond and not the 3,4-bond, i.e., that bond that has the most double bond character is eclipsed. This has been confirmed even for methylfurans, one methyl C—H always eclipsing the 2,3-bond, in contrast to the situation in toluene where the methyl group rotates with almost complete freedom. Microwave data give  $\sim 5$  kJ/mol for the methyl furan rotational barrier. The tendency of all conjugated substituents to lie in-plane is clearly seen, the preferences for *cis* or *trans* conformations correctly deduced, and the generally small nature of simple bulk steric effects (compared with benzene examples) confirmed.<sup>358</sup>

An infrared study including 2-furyl *t*-butyl ketone furnished evidence for changes in both ring and carbonyl stretching bands that could well signal an increasing tendency for the bulkier substituents to rotate out-of-plane. The study is of special interest because it is based not only upon vibrational frequencies, as is common, but mainly upon intensities, which is not. In the *t*-butyl ketone, the carbonyl stretching frequency and its intensity ( $1662\text{ cm}^{-1}$ ; A 6,500) are both lower than in the methyl ketone ( $1674\text{ cm}^{-1}$ ; A 10,500).<sup>357</sup>

Restricted rotation in the amide and thioamide groupings is affected by attachment to a heterocyclic ring, electron release from which raises the energy barrier. The barrier is higher in amides than in equivalent pyrroles, furans, or thiophenes; it is higher in 2-furyl than in 3-furyl compounds.<sup>373</sup> Interactions between the furan ring and attached (*E*)- and/or (*Z*)-alkene groupings have received marked attention,<sup>341,342,374,375</sup> but oxime and imine groupings have not.<sup>376,377</sup>

## B. ELECTRONIC STRUCTURE: SPECTROSCOPY

### 1. General

Let us consider, how MO calculations may be able to assist the interpretation of furan chemistry. Using *ab initio* calculations John and Radom<sup>358</sup> obtain for furan bond lengths and angles very close to those established by microwave spectroscopy (structures **223** and **234**), but the dipole moment is underestimated.<sup>378</sup> In contrast to pyrrole, furan normally has its negative terminus at the oxygen end of the molecule,<sup>379,380</sup> although some substituents can reverse this sense.<sup>135</sup> On the other hand, Simons and Talaty find that the FGSO method with a minimal basis set gives for furan a dipole moment closer to that observed than any other method but that the orbital energies are inferior.<sup>381</sup>

<sup>373</sup> F. Bernardi, L. Lunazzi, P. Zanirato, and C. Gerioni, *Tetrahedron* **33**, 1337 (1977); M. Davis, R. Lakhan, and B. Turner, *J. Org. Chem.* **41**, 2591 (1976).

<sup>374</sup> A. Perjessy, D. W. Boykin, L. Fisera, A. Krutosikova, and J. Kovac, *J. Org. Chem.* **38**, 1807 (1973); M. Cernyova, J. Kovac, M. Dandarova, and D. Rajniakova, *Collect. Czech. Chem. Commun.* **42**, 347 (1977); D. Vegh, J. Kovac, M. Dandarova, and P. Zalupsky, *ibid.*, 889; J. Stetinova, J. Kovac, J. Sura, and M. Dandarova, *ibid.*, 2201; G. Scarlata and M. Torre, *J. Heterocycl. Chem.* **13**, 1193 (1976); see also Ref. 374a.

<sup>374a</sup> A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tamelli, *J. Org. Chem.* **39**, 3595 (1974); A. Arcoria, S. Fisicella, G. Scarlata, and D. Sciotto, *ibid.*, 3025; A. F. Popov, L. I. Kostenko, V. V. Krarchenko, and D. Vegh, *Zh. Org. Khim.* **15**, 367 (1979).

<sup>375</sup> A. Jurasek, V. Knoppova, M. Dandarova, J. Kovac, and L. Reinprecht, *Tetrahedron* **34**, 1833 (1978).

<sup>376</sup> R. Wasylshen and T. Schaefer, *Can. J. Chem.* **50**, 274 (1972).

<sup>377</sup> P. Dev, J. S. Sandhu, and G. Thyagarajan, *J. Heterocycl. Chem.* **16**, 1073 (1979).

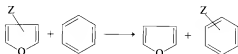
<sup>378</sup> M. H. Sirvetz, *J. Chem. Phys.* **19**, 1609 (1951).

<sup>379</sup> G. Marino, *J. Heterocycl. Chem.* **9**, 817 (1972); T. J. Benton, R. H. Roth, and J. E. Verkade, *J. Am. Chem. Soc.* **94**, 8854 (1972).

<sup>380</sup> F. Fringuelli, S. Gronowitz, A.-B. Hörnfeldt, and A. Taticchi, *J. Heterocycl. Chem.* **11**, 827 (1974).

<sup>381</sup> G. Simons and E. R. Talaty, *J. Am. Chem. Soc.* **99**, 2407 (1977); M. Scholz, N. Fuhrmann, and K. H. Pokrandt, *Z. Chem.* **15**, 401 (1975).

John and Radom<sup>358</sup> also report theoretical stabilization energies for a wide variety of substituents, obtaining them by the method of isodesmic substitution, in which the following hypothetical reaction is analyzed for its energy changes:



Groups as disparate as alkyl, methoxyl, acetyl, and lithium all stabilize furan relative to benzene; nitro and cyano groups destabilize it. In addition to details of conformations and charge distributions for some 30 monosubstituted furans, this paper provides a particularly good bibliography for calculations. Another series of HMO calculations with geometry-optimized furan derivatives<sup>382</sup> is less extensive but includes halogen derivatives not considered by John and Radom, while a third surveys the mono-, di-, and trialkyl furans by HMO-Del Re methods.<sup>383</sup> These studies offer correlations between theory and reactivities, chemical shift, ionization potentials, and other physicochemical properties. Other papers include one not primarily chemical in content<sup>384</sup> and two that demonstrate the power of even very simple calculations to give useful results.<sup>385,386</sup> Indeed, one concerns itself only with the interaction between the  $p_z$  AO of the oxygen atom and the LUMO of the rest of the furan molecule viewed as a butadiene moiety.<sup>386</sup> A comparison of PPP calculations with others including *ab initio* and other semiempirical methods has been made for furan.<sup>387</sup>

## 2. Aromaticity

Furan is included in general accounts of the aromaticity of heterocycles.<sup>388</sup> Newer investigations<sup>389</sup> continue to support the idea that unshared electrons on oxygen are delocalized into a  $\pi$ -orbital covering all five nuclear atoms, so

<sup>382</sup> Y. Rodriguez Gutierrez, C. Aguiar Punal, and L. A. Montero Cabrera, *CENTRO, Ser.: Quim. Tecnol. Quim.* **5**, 3 (1977).

<sup>383</sup> J. Srogl, M. Janda, I. Stibor, V. Skala, P. Trska, and M. Ryska, *Collect. Czech. Chem. Commun.* **39**, 3109 (1974); J. Stibor, P. Trska, J. Srogl, and M. Janda, *ibid.* **43**, 2170 (1978).

<sup>384</sup> R. Aroca, N. Mercieu, and D. Scherson, *Rev. Latinoam. Quim.* **6**, 112 (1975); M. M. Campos Valette, *ibid.* **7**, 99 (1976); Y. Ohrn, *NATO Adv. Study Inst. Ser., Ser. C* **46**, 317 (1978).

<sup>385</sup> Mahanti, M. K. *Indian J. Chem., Sect. B* **15B**, 168 (1977).

<sup>386</sup> N. D. Epitotis, W. R. Cherry, F. Bernadi, and W. J. Hehre, *J. Am. Chem. Soc.* **98**, 436 (1976).

<sup>387</sup> D. R. Land, *Diss. Abstr. Int., B* **36**, 3907 (1976).

<sup>388</sup> M. J. S. Dewar, *Pure Appl. Chem.* **44**, 767 (1975); M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.* **17**, 255 (1974).

<sup>389</sup> Yu. A. Zhdanov, B.-Yu. Khal'mer, L. N. Mazalov, A. T. Shrevaev, P. I. Vadesh, and O. E. Shelepin, *Zh. Strukt. Khim.* **18**, 677 (1977).



furan is almost always described as aromatic. But the extent to which it is aromatic is another question depending, as usual, upon the criterion of aromaticity used. Opinions vary widely.

Fringuelli *et al.* have examined seven measures of aromaticity in a critical fashion.<sup>390</sup> These include (i) NMR dilution shifts using the equation  $A = \Delta\delta_1 V_m^{2/3}$  ( $\Delta\delta_1$  is the difference between chemical shifts of aromatic protons in the pure liquid and at infinite dilution;  $V_m$  is the molar volume of the compound), (ii) the difference in chemical shifts between protons at position 2 and position 3, (iii) bond length and/or bond order differences, (iv) Julg parameters (based on bond lengths but allowing for  $\pi$ -electron circulation), and (v) mesomeric (as opposed to molecular) dipole moment, which for furan is estimated as 1.03 D.<sup>391</sup> For the series furan, thiophene, selenophene, and tellurophene these measures place the members in various orders; most commonly furan is the least aromatic. A surprise is that some measures indicate tellurophene to be considerably aromatic, as indeed its chemistry appears to confirm.<sup>392</sup> Many of the factors playing a part in determining aromaticity conflict with each other; the listed measures are in fair mutual agreement in contrast to a measure utilizing diamagnetic exaltation susceptibility which is widely at variance with them. Furan is weakly aromatic according to Burnham *et al.*<sup>393</sup> who considered local and nonlocal magnetic susceptibilities which categorize furan as aromatic and the pyrones as nonaromatic. A third study sustains the view that furan is about as aromatic as the benzoquinones but that the pyrones are not aromatic.<sup>394</sup>

A substantially different view is afforded by a consideration of heats of atomization and of HMO  $\pi$ -resonance energies. This leads to a close correlation between the observed value for furan (61.70 eV) and the calculated value (61.64).<sup>395</sup> Dewar and his colleagues<sup>396</sup> assign to furan an  $E_R$  value of only 6.7 kJ/mol.

Calculations concerned with the modifications produced in furan by protonating oxygen<sup>396a</sup> or carbon<sup>396b</sup> were considered in Section III,B of

<sup>390</sup> F. Fringuelli, G. Marino, A. Taticchi, and G. Grandolini, *J. C. S. Perkin II*, 332 (1974).

<sup>391</sup> H. Lumbroso, D. M. Bertin, F. Fringuelli, and A. Taticchi, *J. C. S. Chem. Commun.*, 343 (1973).

<sup>392</sup> F. Fringuelli and A. Taticchi, *J. C. S. Perkin I*, 199 (1972).

<sup>393</sup> A. K. Burnham, J. Lee, T. G. Schmalz, P. Beak, and W. H. Flygare, *J. Am. Chem. Soc.*, **99**, 1836 (1977).

<sup>394</sup> J.-i. Aihara, *J. Am. Chem. Soc.*, **98**, 2750 (1976).

<sup>395</sup> B. A. Hess, L. J. Schad, and C. W. Holyoke, *Tetrahedron*, **28**, 3657 (1972).

<sup>396</sup> M. J. S. Dewar, A. J. Harget, and N. Trimajstic, *J. Am. Chem. Soc.*, **91**, 6321 (1969).

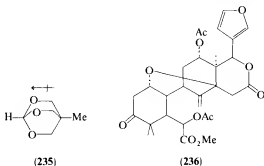
<sup>396a</sup> F. Bernadi, *Gazz. Chim. Ital.*, **107**, 55 (1977).

<sup>396b</sup> M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritsky, P. Linda, and R. D. Tack, *Tetrahedron*, **32**, 1767 (1976).

Part I. The effect of combining furan with alkene and benzene rings has been considered as has the condensation of furan with other furan rings to produce a variety of aromatic systems, some of which have been little explored.<sup>397</sup>

### 3. NMR Studies: Ring Currents

Neglect of the polarization in the  $\sigma$ -bond system of furan and the resulting magnetic anisotropy requires the assumption of a ring current to explain the observed shielding.<sup>398</sup> Whether the ring current is comparable to that in benzene is still not entirely settled, although it is generally thought to be about half the value.<sup>398a</sup> Barton, Rothe, and Verkade<sup>399</sup> have used the orthoester 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**235**) to signal the ring currents in several solvents including furan. Furan molecules are believed to line up so that their  $\pi$ -clouds face the positive end of the dipolar test molecule while at the other end their edges are presented to the methine proton. Compared with the shifts in tetrachloromethane, therefore, the shifts in furan show shielding of the methyl group (0.42 ppm) and deshielding of the methine proton (0.35 ppm). For benzene as solvent these two values are 0.79 and 0.37, respectively, and for cyclopentadiene, 0.37 and 0.14. Tellurophen again emerges as markedly aromatic, much more so than furan.<sup>399</sup> Section VI,B records other examples of shielding by the furan nucleus. In limonoid furans (e.g., **236**) one acetoxy methyl group resonates at  $\delta$  1.82, about 0.4 ppm



<sup>397</sup> J. W. van Reijendam and M. J. Janssen, *Tetrahedron* **26**, 1303 (1970); M. Milun and N. Trinajstić, *Croat. Chem. Acta* **49**, 107 (1977).

<sup>398</sup> I. Juchnovski and J. Kaneti, *Tetrahedron* **27**, 4269 (1971).

<sup>398a</sup> P. Politzer, R. A. Donnelly, and K. C. Daiker, *J. Chem. Soc. Chem. Commun.*, 617 (1973); P. Politzer and H. Weinstein, *Tetrahedron* **31**, 915 (1975).

<sup>399</sup> T. J. Barton, R. W. Roth, and J. G. Verkade, *J. C. S. Chem. Commun.*, 1101 (1972).

higher field than usual; this shift is also attributed to the influence of a nearby furan ring.<sup>400</sup>

Earlier attempts to correlate electron density, etc. with chemical shifts were not very effective,<sup>401</sup> but currently it is proving possible to obtain correlations giving a better insight into the nature of the chemical shift and its components.<sup>383,402-405</sup>

We note some references giving useful long range couplings.<sup>338,363,364,369,405a,406</sup> LIS techniques used with furan compounds,<sup>407</sup> of course, but are of no immediate consequence because the furan oxygen atom is an extremely poor site for complexation.<sup>408</sup> An interesting comparison between the proton spectra of 3-furanones and those of parallel dihydropyrones has been made.<sup>125</sup>

The use of <sup>13</sup>C-NMR spectroscopy is now routine in the structure determination of natural products and has been reviewed for furans and butenolides by Wehrli and Nishida.<sup>409</sup> Some papers already noted in other contexts contain typical examples of work with the carbon isotope,<sup>326,329,400,409a</sup> and a few others are mentioned as more recent than those in the review.<sup>410</sup> Studies concerned with other than naturally occurring furans have also been alluded to already.<sup>95,362,366,377,410a</sup> and exocyclic methylenefuran might also be mentioned<sup>245</sup> along with some typical tetrionic acids.<sup>170,190</sup> More theoretical studies have been concerned with deriving Hammett parameters,<sup>411</sup> substituent interactions,<sup>412</sup> charge distribution in furylcarbenium

<sup>400</sup> D. A. H. Taylor, *J. C. S. Perkin I*, 437 (1974); J. D. Connolly, D. A. Okorie, and D. A. H. Taylor, *ibid.*, 1145 (1972).

<sup>401</sup> P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.*, **20**, 1325 (1967).

<sup>402</sup> G. Pouzard and M. Rajzmann, *Org. Magn. Reson.*, **8**, 271 (1976).

<sup>403</sup> K. A. K. Ebrahim, G. A. Webb, and M. Witanowski, *Org. Magn. Reson.*, **8**, 317 (1976).

<sup>404</sup> F. Fringuelli, S. Gronowitz, A.-B. Hornfeldt, I. Johnson, and A. Taticchi, *Acta Chem. Scand., Ser. B* **28B**, 175 (1974).

<sup>405</sup> W. B. Smith and T. W. Proulx, *Org. Magn. Reson.*, **8**, 567 (1976).

<sup>405a</sup> J. P. Kutney, H. W. Hanssen, and C. V. Nair, *Tetrahedron*, **27**, 3323 (1971).

<sup>406</sup> M. L. Martin, J.-C. Roze, and G. J. Martin, *Tetrahedron Lett.*, 3407 (1970).

<sup>407</sup> G. Montaudo, S. Caccamese, V. Librando, and P. Maravigna, *Tetrahedron*, **29**, 3915 (1973); S. Nagata, T. Yamabe, K. Yoshikawa, and H. Kato, *ibid.*, 2545; P. Camps, J. Font, and J. M. Marques, *ibid.*, **31**, 2581 (1975).

<sup>408</sup> H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971).

<sup>409</sup> F. W. Wehrli and T. Nishida, *Prog. Chem. Nat. Prod.*, **36**, 1 (1979).

<sup>409a</sup> A. Hoppmann and P. Weyerstahl, *Tetrahedron*, **34**, 1723 (1978).

<sup>410</sup> T. Sato, M. Tada, and T. Takahashi, *Tetrahedron Lett.*, 3895 (1977); J. C. Coll, S. J. Mitchell, and G. J. Stokic, *ibid.*, 1539; J. R. Hanson and H. J. Wadsworth, *J. C. S. Chem. Commun.*, 360 (1979).

<sup>410a</sup> D. Florentin, B. P. Roques, and M. C. Fournie-Zaluski, *Bull. Soc. Chim. Fr.*, 1999 (1976).

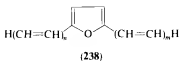
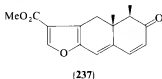
<sup>411</sup> G. Dana, O. Convert, J.-P. Girault, and E. Mulliez, *Can. J. Chem.*, **54**, 1827 (1976).

<sup>412</sup> M. T. W. Hearn, *Aust. J. Chem.*, **29**, 107 (1976).

ions,<sup>413</sup> the orientation of furan in the nematic phase,<sup>414</sup> and problems of aromaticity in comparison with benzene and thiophene.<sup>383,404,405</sup>

#### 4. UV Spectra

Since simple furans absorb close to 220 nm the band is not very useful, and the Cotton effect of the system is correspondingly limited.<sup>415</sup> Conjugation usually shifts the main band into a more reliable region; illustrations among naturally occurring furans include lactaral, a furan-3-carbaldehyde<sup>416</sup>; pukalide (**181**) a furan-3-carboxylate as well as a butenolide<sup>292</sup>; warburgin, with a 3-carboxylate group but with a main chromophore consisting of a dienone group at position 2 as in **237**<sup>417</sup>; and a eremophilane furan with a propenoyl group at position 2.<sup>418</sup> Several authors have commented on the UV spectra of furans incorporated in cyclophane systems (see Section V.B),<sup>248,268,280,283</sup> and steric effects in plant furyl ketones.<sup>352</sup> Czech groups have furnished many spectra of nitrofurans<sup>375,419</sup> and arylthiofurans, some quite complex.<sup>420,421</sup> Arylfurans are still mainly the 2-isomers,<sup>368,421a</sup> but Galasso and Trinajstić<sup>370</sup> have now systematically examined a series of bifurans and congenors including all possible links (i.e., 2,2<sup>1</sup>; 2,3<sup>1</sup>; 3,2<sup>1</sup> and 3,3<sup>1</sup>). Russian authors find that the second-order rate constant for replacement of the halogens by dimethylamine correlates with differences in UV spectra as well as IR and NMR spectra.<sup>422</sup> A study of a series of 2,5-dialkenylfurans (**238**) confirms that, with regard to the main chromophore, the furan ring can be regarded as equivalent to a butadiene



<sup>413</sup> D. A. Forsyth and G. A. Olah, *J. Am. Chem. Soc.* **101**, 5309 (1979).

<sup>414</sup> E. E. Burnell, M. A. J. Sweeney, and T. C. Wong, *Chem. Phys. Lett.* **39**, 389 (1976).

<sup>415</sup> D. L. Dreyer, *Tetrahedron* **24**, 3273 (1968).

<sup>416</sup> G. Magnusson and S. Thoren, *Tetrahedron* **30**, 1431 (1974).

<sup>417</sup> C. J. W. Brooks and G. H. Draffan, *Tetrahedron* **25**, 2865 (1969).

<sup>418</sup> L. Rodriguez-Hahn, A. Guzman, and J. Romo, *Tetrahedron* **24**, 477 (1968).

<sup>419</sup> I. Sroková, A. Jurasek, M. Dandarova, and J. Kovac, *Collect. Czech. Chem. Commun.* **43**, 3252 (1978).

<sup>420</sup> A. Krutosikova, J. Sura, J. Kovac, and S. Juhas, *Collect. Czech. Commun.* **40**, 3362 (1975).

<sup>421</sup> R. Kada, A. Jurasek, and J. Boleha, *Collect. Czech. Chem. Commun.* **42**, 3417 (1977).

<sup>421a</sup> D. C. Ayres and J. R. Smith, *J. Chem. Soc. C*, 2737 (1968).

<sup>422</sup> V. N. Novikov and S. V. Borodacv, *Khim. Geterotsikl. Soedin.*, 1316 (1976).

unit.<sup>423</sup> A few UV spectra have been reported for 3-furanones<sup>187</sup> and acyltetronic esters.<sup>175</sup> Photochemical aspects of UV absorption are considered in Section I.

### 5. Mass Spectra: Ionization Potentials

In addition to MO calculations mentioned previously,<sup>380,382,383,396,423a</sup> others deal with energy levels within furan and similar nuclei either specializing in these<sup>424,425</sup> or treating them in a more general context.<sup>426,427</sup> All include discussions of ionization potentials; the special case of the hydroxyfurans<sup>75,113</sup> has also been mentioned (Sections III,A and B). Electrochemical one-electron oxidation is mentioned in Section VI,A1 (Part I).

During the period under review little has emerged to modify or extend the conclusions from earlier studies; most mass spectra have been obtained as part of the general procedure for determining the structures of natural products and have not been subject to detailed analysis. Many examples are provided by the work of Bohlmann and his associates, for example, the *Athanasia* sesquiterpene furans.<sup>428</sup> The dimers and oligomers formed by condensing furans with aldehydes or ketones are particularly amenable to mass spectrometry,<sup>429</sup> and the technique has proved most useful for probing the structure of the polymer formed by treating specifically labeled [<sup>14</sup>C]-sorbitose with acids. As a result, it is now believed that the initial product is the furyl ketone  $[C_4H_3O]COCH_2OH$  which condenses with itself to give the product (239); the diagram indicates the points of breakage and the products (2H is added as appropriate).<sup>430</sup> Usually the furan ring is a stable structural feature, so much that furans are often thought to be products of mass spectral collapse. Holmes and Terlouw find that 2-pyrone and 4-pyrone collapse to give predominantly  $[furan]^+$  fragment ions, along with some vinylketene ions corresponding to  $CH_2=CHCH=C=O$ .<sup>431</sup> They note that it is unsafe

<sup>423</sup> J. W. van Reijndam, G. J. Heeres, and M. J. Janssen, *Tetrahedron* **26**, 1291 (1970).

<sup>423a</sup> F. P. Colonna, G. Distefano, M. Guerra, D. Jones, and A. Modelli, *J. Chem. Soc. Dalton*, 2037 (1979).

<sup>424</sup> M. Hehenberger, *Chem. Phys. Lett.* **46**, 117 (1977).

<sup>425</sup> Nishijim, Chiho, K. Ohno, H. Nakayama, and Y. Harada, *Joshi Eiyo Daigaku Kiyo* **7**, 41 (1976).

<sup>426</sup> W. von Niessen, L. S. Cederbaum, and W. P. Kraemer, *J. Electron Spectrosc. Relat. Phenom.* **8**, 179 (1976).

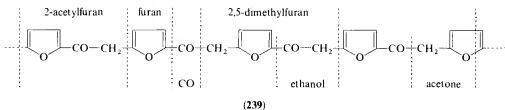
<sup>427</sup> K. Okazaki, M. Yamabe, and S. Sato, *Bull. Chem. Soc. Jpn.* **50**, 1409 (1977).

<sup>428</sup> F. Bohlmann and N. Rao, *Tetrahedron Lett.*, 1039 (1972).

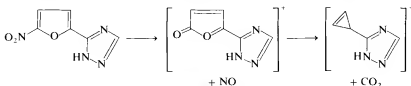
<sup>429</sup> P. H. Boyle, W. Cocker, T. B. H. McMurray, and A. C. Pratt, *J. Chem. Soc. C*, 1993 (1967); E. D. Loughran, F. M. Wewerke, and C. J. Hammons, *J. Heterocycl. Chem.* **9**, 57 (1972).

<sup>430</sup> K. Heyns and R. Hauber, *Justus Liebig's Ann. Chem.* **733**, 159 (1970).

<sup>431</sup> J. L. Holmes and J. K. Terlouw, *J. Am. Chem. Soc.* **101**, 4973 (1979).



to give firm structural assignments to such ions under conditions where these have enough internal energy to fragment; previous work using isotopic labeling had suggested that the metastable ions from 2-pyrone do not undergo (reversible) ring closure to furan species.<sup>432</sup> Nitrofurans are less stable than others, collapse of the nitrofuran ring being the main feature (Scheme 72).<sup>433</sup>



SCHEME 72

Suitable "ortho" substituents may allow eliminations to occur within the mass spectrometer, and then the furan ring need not survive. Scheme 73A shows a simple elimination and Scheme 73B a similar situation in which a furylmethyl fragment cation is thought to expand its ring much as benzylic fragment ions expand to the tropone system. The ring oxygen may be concerned with a characteristic breakdown of  $\alpha$ -ethoxymethyl groups to give acetaldehyde fragments (Scheme 73C).<sup>434</sup> A large number of aryl-furan<sup>434a</sup> and pyridylfuran<sup>434b</sup> mass spectra have been recorded by Czech workers. Studies of the mass spectral collapse of tetrone acid derivatives have also been made.<sup>345,435</sup>

The polarizability of furan has received some attention,<sup>436</sup> but charge transfer phenomena have proved more interesting. CNDO/2 calculations

<sup>432</sup> W. Pirkle and M. Dines, *J. Am. Chem. Soc.* **90**, 2318 (1968).

<sup>433</sup> Y. Kato and I. Hirao, *Bull. Chem. Soc. Jpn.* **45**, 1876 (1972).

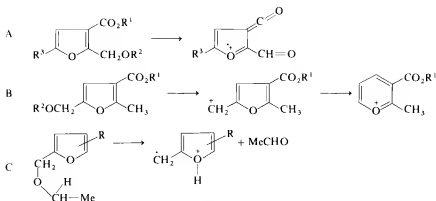
<sup>434</sup> V. Kubelka, J. Mitera, and M. Valenta, *Collect. Czech Chem. Commun.* **36**, 4082 (1971).

<sup>434a</sup> L. Fiserá, J. Kovac, E. Komanova, and J. Lesko, *Tetrahedron* **30**, 4123 (1974); L. Fiserá, J. Lesko, J. Kovac, and B. Hasova, *Collect. Czech Chem. Commun.* **41**, 3398 (1976); A. Krutskikova, J. Kovac, and V. Sykora, *ibid.* **39**, 1892 (1974).

<sup>434b</sup> L. Fiserá, J. Lesko, J. Kovac, J. Hrabovsky, and J. Sura, *Collect. Czech. Chem. Commun.* **42**, 105 (1977).

<sup>435</sup> R. L. Edwards and M. Gill, *J. C. S. Perkin I*, 1921 (1973).

<sup>436</sup> B. P. Rao, *Indian J. Pure Appl. Phys.* **14**, 276 (1976); D. H. Sutter and W. H. Flygare, *J. Am. Chem. Soc.* **91**, 4063 (1969).



SCHEME 73

have been made of the stabilization energies and intermolecular distance in furan-tetracyanoethene complexes<sup>437</sup>; similar complexes with chloranil and maleic anhydride have been studied.<sup>438</sup> The furan-TCNE complex exhibits two new electronic absorption bands, one near 445 nm correlates with the ionization potential of the donor. The other band (near 295 nm) if it does not originate in the acceptor might arise from an internal orbital of the donor.<sup>438</sup> Complexes formed between TCNE and furans containing silyl, germyl, stannyl, and plumbyl substituents have indicated for the Group IVA elements the order of electronegatives  $C < Si > Ge > Sn > Pb$ , the high electronegativity of silicon resulting from  $d-p$  interactions with the heterocycle.<sup>439</sup>

## C. REACTIVITY

### 1. General

Several specific questions of structure-reactivity relationships have been considered here, including MO calculations as well as NMR, UV, and IP data.<sup>358,380,383,439a</sup> Whereas it has been usual to take a proton as a typical electrophile or to ignore the actual attacking species altogether, Decoret

<sup>437</sup> A. Z. Dzhumanazarova, I. A. Abronin, V. P. Litvinov, G. M. Zhidomirov, and V. A. Korsumov, *Khim. Geterotsikl. Soedin.*, 1956 (1979).

<sup>438</sup> Z. Yoshida and T. Kobayashi, *Tetrahedron* **26**, 267 (1970); A. R. Cooper, C. W. Crowne, and P. G. Farrell, *Trans. Faraday Soc.* **62**, 18 (1966).

<sup>439</sup> M. A. Lopatin, V. A. Kuznetsov, A. N. Egorochkin, O. A. Pudova, N. P. Erchak, and Z. Ia. Pukevits, *Dokl. Akad. Nauk SSSR* **246**, 379 (1979).

<sup>439a</sup> D. Chou and H. Weinstein, *Tetrahedron* **34**, 275 (1978).

and Tinland<sup>440</sup> find that by including in HMO calculations a parameter to characterize the electrophile they can account for variations in the site of attack.

The relative sensitivity of furan to electrophilic attack stands in the order benzene < naphthalene < ferrocene < furan as found from competition experiments with styrene palladium(II) acetate.<sup>441</sup> Relative rates for acylation by trifluoroacetic anhydride (no catalyst) are observed to be thiophene (1), selenophene (6.5), furan ( $1.4 \times 10^2$ ), pyrrole ( $5.3 \times 10^7$ ), and 2-methylfuran ( $1.2 \times 10^5$ ).<sup>442</sup>

## 2. Hammett Correlations

In making Hammett correlations furan is assumed to be benzene-like. This assumption may not always be valid (cf. Section IIIA, Vol. 30). Problems stem from the existence in furan of *two* meta geometries, (240a and 240b), whereas in benzene there is but one, and the ambiguity presented by the furan oxygen atom. If the oxygen atom is "not counted," then 2,5-disubstitution is equivalent to para disubstitution in benzene. But if the oxygen atom counts as "one atom," then 2,5-substitution could be regarded as a meta as well as para. Feraz and Amaral, who determined acidity constants for a series of 5-substituted 3-furoic acids, found that very good correlations could be obtained with both the meta and the para (benzene) substituents constants, and the  $\rho$  value indicated a larger transmission of effects through the furan than through the benzene ring.<sup>443</sup> A similar situation is found with 5-substituted 2-furylacrylic acids.<sup>420,444</sup> Noyce and Pavez<sup>445</sup> find that in 5-substituted furfuryl systems resonance interaction is nearly the same as for para-substituted benzenes when employing the  $\sigma_p^+$  substituent parameter. Moreover, while the 4-substituted furfuryl system shows less resonance interaction, it is nevertheless greater than the corresponding meta interaction in benzene. They also find that satisfactory correlations are obtained by the use of Brown  $\sigma^+$  constants; furan is very sensitive to substituents, as reflected in a large value for  $\rho$  (about  $-8$ ). In the "meta" situation with 5-substituted 3-furylmethyl systems a similar large  $\rho$  value is indicated; this is to be compared with a benzene value of 2 or 3.<sup>445</sup>

<sup>440</sup> C. Decoret and B. Tinland, *Aust. J. Chem.* **24**, 2679 (1971).

<sup>441</sup> Y. Fujiwara, R. Asano, I. Maritani, and S. Teranishi, *J. Org. Chem.* **41**, 1681 (1976).

<sup>442</sup> S. Clementi and G. Mariano, *Tetrahedron* **25**, 4599 (1969).

<sup>443</sup> J. P. Ferraz and L. do Amaral, *J. Org. Chem.* **41**, 2350 (1976).

<sup>444</sup> J. Kovac, J. Stetinova, J. Sura, F. Spacek, and R. Brezny, *Collect. Czech. Chem. Commun.* **42**, 1871 (1977).

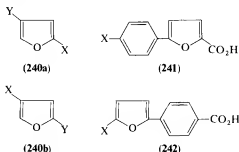
<sup>445</sup> D. S. Noyce and H. J. Pavez, *J. Org. Chem.* **37**, 2620, 2623 (1972).



Solvolyses data for 5-substituted 2-furylmethanol derivatives have been correlated.<sup>446</sup> Results for arylation fit Hammett plots using  $\sigma^+$  values provided that the aryl radical contains strongly polar substituents such as nitro or halogen.<sup>446a</sup> Another correlation involves eliminations in 1-(2-furyl)-ethyl acetate to give furyl alkenes.<sup>447</sup> The furan ring itself has been assigned a  $\sigma$  value.<sup>434b</sup>

### 3. Transmission Factors

Czech workers have taken advantage of the ease with which 2,5-disubstituted furans can be synthesized to make numerous studies of the transmission of electronic effects through the furan ring as, for example, in a series of acids such as **241**<sup>448</sup> and **242**.<sup>449</sup> Correlations between  $pK_a$  values and substituent



constants are good except for ortho substituents able to prevent coplanarity of furan and benzene ring systems.<sup>448</sup> Transmission factors given by the ratio of  $\rho$  values for furan to benzene are proposed for use in correlation studies but seem to vary rather more than is desirable. For the acids (**241**) this parameter is 0.329 from  $pK_a$  measurements and 0.291 from rates of ester hydrolysis.<sup>448</sup> A study correlating substituent effects with ir carbonyl stretching bands in the 5-arylfurfural series shows that the transmission factor is influenced by solvent, being 0.65 in tetrachloromethane and 0.48 in trichloromethane.<sup>450</sup> A few furan derivatives have been subjected to a correlation involving substituent effects and carbonyl stretching frequen-

<sup>446</sup> D. S. Noyce and C. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

<sup>446a</sup> L. Benati, C. M. Camaggi, M. Tiecco, and A. Tundo, *J. Heterocycl. Chem.*, **9**, 919 (1972).

<sup>447</sup> G. G. Smith and J. A. Kirby, *J. Heterocycl. Chem.*, **8**, 1101 (1971).

<sup>448</sup> A. Krutiskova, J. Kovac, J. Rentka, and M. Cakrt, *Collect. Czech. Chem. Commun.*, **39**, 767 (1974); A. Krutiskova, J. Sura, J. Kovac, and K. Kalfus, *ibid.*, **40**, 3357 (1975).

<sup>449</sup> L. Fiser, J. Sura, J. Kovac, and M. Lucky, *Collect. Czech. Chem. Commun.*, **39**, 1711 (1974).

<sup>450</sup> A. Perjessy, R. Frimm, and P. Hrnčiar, *Collect. Czech. Chem. Commun.*, **37**, 3302 (1972).

cies.<sup>451</sup> A series of 2-carboxylic acids from furan to tellurophene and some of their benzo derivatives indicates that acidities are mainly a function of electronegativity, resonance effects being less important.<sup>452</sup> Half-wave potentials obtained at the dropping mercury electrode for carbonyl compounds have been correlated with substituent effects.<sup>452</sup> However, many studies include transmission not only through furan rings but also through sulfide, sulfone, carbonyl, vinyl, and other groupings at the same time and often with complex substituents as well.<sup>374,375,420,453,454</sup> Japanese authors describe the ability of the nitrofuran group to sustain vinylamines in their enamine form, stabilised no doubt by the electronic interaction between the nitro group and amino group.<sup>455</sup>

Similar reactivity studies have been conducted with nucleophilic substitution reactions both at the furan nucleus and at side-chain groupings,<sup>374-375,419,422</sup> the only additional feature being the formation of Meisenheimer complexes in reactions with nitrofurans.<sup>456,456a</sup>

#### D. MISCELLANEOUS

Papers have appeared concerned with (i) the migratory aptitude of 2-furyl relative to vinyl and ethyl groups. In the vapor phase on alumina; the order is the same as that in acidic solvents<sup>457</sup>; (ii) the effect of complexation with  $\text{BCl}_3$  or TCNQ upon the aromaticity of furan,<sup>458</sup> (iii) the molecular rotational Zeeman effect in 3-methylfuran<sup>459</sup>; and (iv) microwave and  $^1\text{H}$ -NMR spectra and the molecular dimensions of furan when held in a nematic phase provided by methoxybenzene azophenylcaproate.<sup>460</sup>

<sup>451</sup> A. Perjesy, *Tetrahedron* **29**, 3189, 3207 (1973).

<sup>452</sup> F. Fringuelli and A. Taticchi, *J. Heterocycl. Chem.* **10**, 89 (1973).

<sup>453</sup> A. Beno, A. Krutosikova, L. Fisera, and R. Frimm, *Collect. Czech. Chem. Commun.* **38**, 2734 (1973).

<sup>454</sup> R. Kada, V. Knoppova, A. Jurasek, and J. Kovac, *Tetrahedron* **32**, 1411 (1976); R. Kada, V. Knoppova, and J. Kovac, *Collect. Czech. Chem. Commun.* **42**, 338,3333 (1977); M. Hrdina, A. Jurasek, and V. Knoppova, *ibid.*, 512; V. Knoppova, A. Jurasek, and V. Voros, *ibid.*, 3175; R. Kada, J. Sura, A. Jurasek, J. Kovac, and A. Zvakova, *ibid.* **43**, 621 (1978); D. Geisbacher, A. Jurasek, M. Dandarova, and J. Kovac, *ibid.*, 1618.

<sup>455</sup> A. Tanaka, T. Usui, and S. Yoshina, *J. Heterocycl. Chem.* **15**, 515 (1978).

<sup>456</sup> G. Doddi, F. Stegel, and M. T. Tanesi, *J. Org. Chem.* **43**, 4303 (1978).

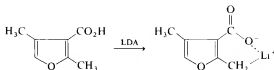
<sup>456a</sup> G. Doddi, A. Poretti, and F. Stegel, *J. Heterocycl. Chem.* **11**, 97 (1974).

<sup>457</sup> G. Dana and J. Wiemann, *Bull. Soc. Chim. Fr.*, 3894 (1970).

<sup>458</sup> Ya. M. Kimel'fel'd, L. M. Mostovaya, B. P. Bespalov, and V. V. Titov, *Teor. Eksp. Khim.* **12**, 241 (1976).

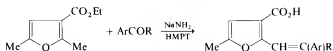
<sup>459</sup> W. Czieslik, J. Wiese, and D. H. Sutter, *Z. Naturforsch., A* **31A**, 1210 (1976).

<sup>460</sup> P. Diehl, C. L. Khetrapal, and H. P. Kellerhaus, *Helv. Chim. Acta* **51**, 529 (1968).



SCHEME 74

Scheme 74 shows selective deprotonation of one of two methyl groups that depends upon the presence of an ortho carboxyl,<sup>460a</sup> and Scheme 75 shows a more complex but similar example.<sup>461</sup> Related C—C bond-forming reactions are known.<sup>462</sup> Scrambling of isotope into the methyl group of 5-methyl-2-furoic acid when it is decarboxylated at about 240°C in deuterium oxide<sup>463</sup> probably involves a similar carbon deprotonation. The behavior of furan derivatives in polymerization reactions has been reviewed by Gandini.<sup>464</sup>



SCHEME 75

### ACKNOWLEDGMENT

I thank Drs. F. D. Dean and B. S. Varma for assistance with the collection of the bibliography.

<sup>461</sup> Y. Anghelova, S. Spirova, and C. Ivanov, *Synthesis*, 313 (1977).

<sup>462</sup> Yu. M. Shapiro and V. G. Kul'nevich, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, **56**, 105 (1979).

<sup>463</sup> J. A. Hirsch and D. E. Sterner, *J. Org. Chem.*, **37**, 1678 (1972).

<sup>464</sup> A. Gandini, *Adv. in Polymer Sci.*, **25**, 47 (1977).

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